INTERNAL SECRETION AND THE DUCTLESS GLANDS

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AND THE

DUCTLESS GLANDS

BY

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PREFACE

THE first edition, issued in 1912, has been out of print since 1914, but for various reasons the publication of the second edition has been delayed. During this time many aspects of the subject of internal secretion have undergone material changes. These I hope will find adequate expression in the new version of the book. If I have not been so optimistic and expansive in the treatment of certain topics as other writers on the same subjects, it is because I am convinced that a surer road to sound knowledge lies in the direction of rigid criticism and a reasoned scepticism.

After much doubt and hesitation I have decided to omit the bibliography. The objections to such a course are obvious, but I found that to review the whole of the literature has become impossible, and to make a selection involves a task so invidious and delicate and at the same time laborious that I have not had the courage to attempt it. The omission of the references to literature will, however, have the advantage of making the book easier to read, and for a large number of students and practitioners will, I hope, not constitute a serious drawback. Investigators who have access to the first edition will find no difficulty in completing a survey of the literature up to the present time. The papers since 1917 are abstracted in *Endocrinology*, and since 1915 in *Physiological Abstracts.* Names are still mentioned freely in the text for the reasons that this arrangement involves less re-writing, and that it leaves the responsibility in the hands of the original author on numerous topics in which I have had no opportunity of gaining first-hand information.

The present edition contains much new matter, but, by re-arrangement and some curtailment of historical and controversial sections, it has been possible to avoid increasing the size of the book. The number of illustrations has been increased from 93 to 105. The portions dealing with clinical

subjects have been increased very considerably and this, it is hoped, will make the book more useful to students and practitioners. Many of the new illustrations are photographs of patients suffering from diseases of the organs of internal secretion.

The nucleus of the book was an article in the *Ergebnisse der Physiologie*, and I have to thank the Editor, Professor Asher, of Bern, and the publisher, for their courtesy in allowing me to use the material as the basis of the present work.

Many of the illustrations are derived from papers contributed to various journals from time to time, either by myself, or by or in conjunction with pupils and others working under my direction. A large number have been drawn for me by the late Mrs. F. D. Thompson, of the University of Manitoba. The figures specially drawn by her for the present work are Nos. 13, 13*a*, 29, 56, 91, 92, 93, 95, 104 and 105, while Nos. 9, 10, 11, 57, 77, 79, 80 and 81 were drawn by her to illustrate her paper in the *Phil. Trans.*, 1910.

Most of the tracings have been taken from papers by myself or conjointly produced in the *Journal of Physiology* and *Endocrinology*, and I have to thank Professor Langley for supplying clichés of blocks of many of those published in the former journal. Some of the tracings have, however, been taken from the records of class demonstrations (Figs. 39–43) or from unpublished work in my laboratory (Fig. 46). Figs. 58 and 59 were drawn by Mr. Carmichael from sketches kindly furnished by Professor Evatt.

Diagrams A and B of Figs. 82 and 90 are taken from a paper by Dr. Kohn, of Prag. Figs. 20, 23, 24 and 26 are taken from papers by Giacomini, Fig. 21 from Diamare, and Fig. 22 from Kohn. Figs. 83–86 are borrowed from Murray (*Diseases of the Thyroid Gland*. London, H. K. Lewis, 1900). Fig. 87 from Adami (*Text-book of Pathology*. Lea and Febiger). Figs. 88 and 89 are taken from a paper by Sutherland Simpson. Fig. 98 is a photograph kindly supplied by Dr. Harvey Cushing, while Figs. 99, 100, 101, 102 and 103 are taken from Cushing's book on the Pituitary.[1] For all these I beg to express my best thanks, to both author and publisher.

I have to thank Professors A. T. Cameron and Charles H. O'Donoghue of the University of Manitoba for much assistance,

[1] *The Pituitary Body and its Disorders*, 1912. Lippincott Phila.

Dr. Cramer, of the Imperial Cancer Research Laboratory, for criticism in the chemical portions of the book, and Dr. Leonard Kidd for references to literature. To Mr. Samson Wright I am deeply indebted for his services in the revision of the whole book, and to Mr. J. W. Brown for assistance in the preparation of the index.

I owe a debt of gratitude to Sir Edward Sharpey Schafer for his kindly encouragement and advice on various matters extending over a period of many years. From the time when I had the privilege of acting as his assistant in University College, London, he has always been ready to place the services of his laboratory at my disposal and to assist me in numerous other ways.

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CHAPTER I

INTRODUCTORY—SECRETION AND INTERNAL SECRETION

DURING the last quarter of a century a vast amount of investigation has been carried out upon the subject of internal secretion, and very numerous facts have been accumulated and various theories put forward. Our knowledge of the subject is still in many directions very indefinite, and it will be my duty to adopt a somewhat more sceptical and less optimistic attitude in regard to certain branches of the subject than that adopted by some modern writers. It is desirable, at any rate, that the material should be collected and critically examined, though the task is rendered difficult from the fact that many of the contributions are to be found in obscure and even inaccessible publications.

Before passing on to the discussion of *internal* secretion, it will be well to define as accurately as possible our conception of secretion in the most general sense of the word. In plants as well as animals, in unicellular as well as in multicellular organisms, various substances are formed as a result of the metabolic activities of the living protoplasm. In the unicellular organisms these substances help in the absorption of food material, or serve some other purpose in the economy of the cell, or they are cast away as waste materials into the medium in which the creature lives. In multicellular organisms the materials may be utilized either in the cell itself or in some other part of the body. In the latter case they may be of service to minister either to the proper function of some special apparatus (such, for example, as the digestive tract), or to the

integrity of the entire organism. On the other hand, they may be of no further use in the economy, and may be cast out as waste products.

By the term "secretion," applied in its most general sense, is, or has been, understood the separation out of a substance or of substances from or by the agency of the living protoplasm. This, the original conception of the process, has long been extended to include also the preliminary preparation, or a more or less complete elaboration of the materials which are supplied by the processes of osmosis and diffusion, and in the case of the multicellular organisms by the blood circulating through the organ or tissue.

Johannes Müller pointed out that the whole process of secretion consists of two phases—the production of certain materials and the casting out of these materials upon a surface either in the interior or upon the exterior of the body. The first phase he called "secretion," the second "excretion." In some cases the material eliminated might be found in the blood-stream, and was simply separated by the cells of the organ and passed out. This applied to the urea of the urine, which was looked upon by Müller as a pure case of "excretion." The distinction thus set up has, however, not been maintained by physiologists. The term "excretion" has been, and is at the present time, applied sometimes in a vague kind of way, sometimes more definitely and specifically, to denote the process of elimination of waste products from the body. This process is frequently of the nature of secretion. Thus the elimination of urea by the kidney is referred to as a "secretion," although the product itself is an "excretion." This is due to the fact, now well established, that, although urea is present in the blood supplied to the kidneys, yet it is not simply filtered out of the blood, but is got rid of by a definite "secretory" activity of the cells of the tubules. It can be shown that the cells are capable of performing a definite chemical synthesis, and this is regarded as a sign, or one of the signs, of a "secretory" activity; so that the term "secretion" includes "excretion." When the products of metabolism are of no service in the economy, they are called "excretions."

Among the best known of the secretions are the enzymes and analogous products (such as will be referred to later as the products of the "internal" secretions). But many skeletal

substances are often included in the same category; such are the calcareous shells of the Foraminifera, the chitinous cases of insects, cell membranes, etc. Many authors would include also certain intercellular substances, such as are found in the fibrillar connective tissue, cartilage, and bone. Where, however, definite morphological structures are formed, it will be well not to employ the term "secretion." Thus, the products of the reproductive organs—the ova and spermatozoa—are not to be included in this category.[1]

The term "secretion" in higher animals is ordinarily meant to apply to the liquid or semiliquid products formed by the glandular organs, or to the process of manufacture and setting free of such products. The idea of secretion has, from the earliest period of physiology, been associated with what are called "glandular" organs. The term "gland" was applied in the early days of anatomy to a very varied group of structures which resembled each other only in certain general external characters.[2] Thus, in the same general category were included not only such typical glands as the pancreas, submaxillary glands, and kidneys, but also the liver, spleen, lymph nodules, reproductive organs, and, as they were discovered, the thyroid body, the suprarenal capsule, the thymus, and so on.

There is no need to describe a "gland" in any detail. We may define a gland as a structure made up of one or more cells of a special epithelial character which forms a product, the secretion, which is discharged upon an epithelial surface, such as the skin or a mucous membrane. This is the definition of an ordinary or externally secreting gland.

The simplest type of a gland consists merely of a layer of epithelial cells placed upon a basement membrane, while

[1] The seminal fluid as a whole is, of course, to be looked upon as a secretion coming partly from the testes, but chiefly from the accessory sexual glands. The secretion itself is to be regarded as a vehicle for the transportation of the spermatozoa, and possibly also for their nutrition. But whether or no we view the testis as a gland having an *external secretion*, we shall see reasons later for considering it to be a gland with an *internal secretion*.

[2] "Die Classe der Drüsen ist eine derjenigen welche eine Wissenschaft in ihrer ersten Jugend leichtsinnig schafft, und welche zu begrenzen und rechtfertigen ihr in Zeiten der Reife grosse Sorgen und Mühe kostet. Mann hatte anfangs nur die aüssere Form in Auge und nannte jedes weiche, rundliche, gefässreiche und daher röthliche oder rothe Organ eine Drüse, und das Gewebe solcher Organe drüsig (Henle).

beneath the membrane are found blood capillaries and lymph spaces. When such a layer of epithelial cells becomes invaginated, we have a tubule or saccule possessing a lumen, and forming a simple tubular or saccular gland. Such glands may be coiled, as in the case of the sweat glands, or the secretory portions of the glands may divide, forming branched tubular glands. This branching may occur again and again, until a complicated structure is produced (compound tubular and compound saccular [or racemose] glands). In these glands the terminal portion of the tubes or "alveoli" are the secretory portions, while the tubes leading to the exterior are the "ducts." The gland cell varies in its microscopic appearance, according to its functional condition. In the submaxillary gland and in the pancreas the variations are well known and easily observed—the discharge of the zymogen granules and the resulting changes in the appearance of the secreting cells. Similar functional changes may be observed in the epithelium of the intestine.

But it was discovered that some of these glands possessed no duct, and they were therefore called "ductless glands," or in German more usually "Blutgefässdrüsen," or "Blutdrüsen." The latter names are, however, rapidly falling into disuse, and the terms, "ductless glands," or "glands with an internal secretion," are replacing them. The assumption was at once made that, since these structures had the characters of glands, they must "secrete." But since there was no communication with a free surface, the hypothesis soon arose that in these cases the specific secretion is passed into the blood-stream, and both the process and the product were termed "internal secretion." Thus a new conception in regard to the physiological nature of secretion sprang into existence, and the definition of a gland was extended so as to apply to any structure made up of one or more cells of a special epithelial character which form a product—the secretion—which is discharged upon a free epithelial surface, such as the skin or mucous membrane, or upon the closed epithelial surface of the blood cavities. In some cases the material secreted by the ductless glands has been supposed to be passed away not directly into the blood-stream, but indirectly by means of the lymphatics. This was formerly believed to apply to the specific secretion of the thyroid gland (see, however, p. 307).

In the case of the pituitary it has been supposed that the secretion passes out into the cerebro-spinal fluid.

The "consensus partium" of the older medical writers was supposed by Cuvier to depend on the activity of the nervous system, and upon this alone; but in 1775 Borden put forward the doctrine that each organ has its "humeur particulière" which is necessary to the body as a whole.[1]

The first experimental demonstration of internal secretion was undoubtedly that of Berthold in 1849. This writer describes how he removed the testes from young cockerels and transplanted them to the surface of the intestine, and found that when this was done the young cockerel did not develop in the way that castrated animals usually did, but that they grew into normal cocks. Berthold concluded that the "consensus partium" depends on the fact that the testes affect the blood and the blood affects the whole animal.

The term "internal secretion" was, so far as I can ascertain, first used in 1855 by Cl. Bernard, who described the glycogenic function of the liver as the "sécrétion interne," while he referred to the preparation of the bile as the "sécrétion externe."[2]

The glycogenic function of the liver is not at the present time usually treated among the internal secretions. It is a special kind of arrangement for the storing of food material. The glycogenic function of the liver is, however, intimately related to certain internal secretions—notably those of the pancreas and the adrenal body. Moreover, there are reasons, as we shall see, for attributing to the liver other kinds of internally secreting activities.

Since the time of Cl. Bernard there has been much loose thinking and loose writing upon the whole subject of internal secretion. A great tendency has often been manifested to reach premature and unwarrantable conclusions. In morphology and comparative anatomy ill-understood organs or

[1] According to Gley, Borden does not express himself quite so definitely as some writers have alleged.

[2] "Chez les animaux la sécrétion glycogénique est une sécrétion interne, parce qu'elle se diverse directement dans le sang. J'ai considéré le foie, tel qu'il se présent chez les animaux vertébrés élevés comme un organe sécréteur double. Il semble réunir, en effet, deux éléments sécrétoires distincts et il représent deux sécrétions : l'une externe qui coule dans l'intestin, la sécrétion biliare ; l'autre interne, qui se verse dans le sang, la sécrétion glycogénique.

parts of organs have sometimes been hastily and incorrectly assigned to the group of ductless glands, and in physiology many processes which were imperfectly understood have been prematurely classed among the internal secretions. In the realm of clinical medicine this tendency has been even more marked.

The study of the efficacy of various organs as remedial agents arose in the time of Hippocrates, and Celsus and Dioscorides recommended the use of various animal organs for the relief of those symptoms in man which were considered to be due to defective action of the same organ; hence the use of the pigeon's or wolf's liver in cases of hepatic disease, the brain of the hare for tremors, the lung of the fox for dyspnœa, and the use of rennet for disorders of the stomach and intestines. Pliny recommended the use of the testicles of the donkey and of the stag as aphrodisiacs; and even at the present time there remains the practice of employing castoreum for menstrual disorder.[1]

Much interest was aroused by the work of Brown-Séquard in 1889 upon testicular extracts. This author put forward the theory that all tissues give off something or other to the blood which is characteristic or specific, and which is of importance to the nutrition of the body generally. This may be regarded as the real beginning of the modern doctrine of internal secretion, and represents the actual view of many modern writers, particularly in France. It will be seen that the view of internal secretion which we shall advocate is modified from this, inasmuch as secretion is only to be attributed to certain special cells, and not to all elements in the body.

Brown-Séquard's theory led to a revival of the old humoral physiology, a partial dethronement of the nervous system, and a return to the therapeutic methods called "opotherapy." The "humours" of to-day are, however, very different conceptions from those of the blood, the yellow bile, the black bile, and the phlegm of Hippocrates and Galen. The modern conceptions, indeed, could only have arisen with the growth of modern chemistry. Both physiology and pathology are becoming more and more chemical.

We shall see hereafter how very minute may be the quantities of substances which come into play in physiological actions.

[1] These examples are quoted from Batty Shaw.

The phenomena of chemotaxis, of anaphylaxis, and of the activities of ferments and toxins, all illustrate the importance of the "chemistry of imponderables." Richet lays stress on the significance of individual humoral differences. "Every illness, every intoxication, has caused the formation, perhaps the destruction, of a certain substance in the blood, and has left its natural trace—a trace which is not effaced by years. Just as there is a psychological memory—facts which are present to the consciousness—so there is a humoral memory of all preceding injections. As these injections differ in each person in intensity, quantity, and duration, it follows that each person differs from every other in the chemical properties of his blood."

The irritability which rules the functions of the nervous system is in itself a chemical phenomenon. Richet says: "The living being is a chemical mechanism, and perhaps it is nothing more." Such a sentence by an eminent modern physiologist illustrates the trend of present-day physiology. The attitude is reminiscent of that which became prevalent in the earlier days of Huxley's work. The modern view of "protoplasm" is, however, very different from the original one, and the chemical attitude, critically restrained, may possibly do more to explain the processes of life than all the painstaking anatomical, microscopical, and mechanical investigation of the past fifty years.

The theoretical basis for opotherapy and the practical value of this method of treatment has varied very considerably in different cases. Some flagrant examples of uncritical application of the method are the treatment of heart disease by extracts made from heart muscle, subcutaneous injections of extracts of ciliary bodies in iritis, and of synovial membranes in diseases of the joints.

Long ago the conception was formulated that "each single part of the body, in respect of its nutrition, stands to the whole body in the relation of an excreting organ." The term "excreting" was here used in Johannes Müller's sense (*vide supra*, p. 2), and is practically synonymous with the modern "secretion." It is certain that the organs of the body produce effects upon one another in many different ways by means of the products of their metabolic activity. Conveyed in the blood-stream to different parts of the body, these pro-

ducts may act as agents of augmentation, or possibly inhibition, in regard to the special activities of various organs and tissues. One of the best examples of this is the excitation of the respiratory centre produced during asphyxia by the circulation in the blood of decomposition products normally eliminated in the expired air. Again, when a large amount of protein is absorbed and digested, the products formed probably stimulate an increased metabolism in the body generally. When this occurs, urea is formed by the liver in larger amount, and stimulates the kidneys to increased activity.

In a certain sense, and in the direction just indicated, it is evident that all the tissues and organs of the body form internal secretions, for they all pass into the blood materials which have been formed as products of their metabolism. Everything which an organ or tissue absorbs from the blood and lymph it gives out to them again in some form or other, except in so far as it forms or separates a secretion which passes away by special ducts. It is obvious that in this, the broadest sense of the expression "internal secretion," nothing further is implied than that the blood which leaves by the veins coming from an organ or tissue contains different chemical substances from that which enters by the arteries. A distinction might possibly be made in some cases between *katabolic* products such as are formed by all tissues, and *synthetic* products which are only formed by some, and the term "internal secretion" might be reserved for the latter. But this distinction could not be maintained systematically, for it is quite conceivable that a definite specific and powerful internal secretion might be formed by a katabolic process. Some authors have included intracellular enzymes among the internal secretions. These are still more "internal" than the secretions usually so-called, for they are not passed out of the cell in which they are produced. They differ from the exo-enzymes such as are found in the secretions by reason of the fact that they are bound up in the protoplasm of the cells, and, so long as the cells are alive, can only exert their action intracellularly. When the cells die the protoplasm breaks up, and the enzymes may pass into solution. It is supposed that these enzymes are elaborated by and used during the life of the protoplasm. It is possible that in starvation they may bring about the solution of the tissue proteins, and that the autolytic processes which take place

after death are due to their activity. It has been suggested that life is nothing more than the sum-total of the activities of the enzymes contained within the living matter. A theory related to this has been suggested in a tentative form by Bayliss and Starling. In a paper on the mechanism of pancreatic secretion (a subject which will be referred to again later on, *vide infra*, p. 59), these authors tested the hypothesis that the products of metabolism of certain tissues would be found to act as vasodilators only for certain tissues in functional relation to those in which they arise, or, at all events, would act to a greater degree on these tissues than on the rest of the body in general. Results were obtained which tended to confirm their view. Vincent and Sheen, however, obtained different results, and suggested that the subject may be complicated by the existence not only of specific vasodilators, but also of specific vasoconstrictor substances, whose effects might be looked for on those occasions when the injection of a tissue extract produces a rise of blood-pressure. This line of work has, however, not led to any definite conclusions.

In some modern textbooks the conception of internal secretion is extended beyond the limits which appear reasonable. Thus, it is stated that the lymphatic glands "form an internal secretion which consists of lymph cells, and these furnish the blood with a supply of certain kinds of colourless corpuscles." It has already been mentioned (*supra*, p. 3) that definite morphological elements should be excluded from the category of the secretions. Thus, the ova and spermatozoa are not included among the external secretions, and the cells manufactured by the spleen, lymph glands, and bone-marrow must be excluded from the group of internal secretions.

The conception of internal secretion has had far-reaching effects in the realms of both physiology and pathology. Pathologists are now able to recognize the existence of new forms of stimuli which influence growth and metabolism, and this either in a positive or in a negative direction—that is to say, either in the direction of augmentation or inhibition. Thus, to mention one example, dwarfism and gigantism may be explained by reference to certain internal secretions, or, at any rate, a plausible hypothesis may be furnished by such reference. It is further to be noted that the function of each particular internally secreting gland may be conceived as varying, or capable of

varying, from the normal in the sense either of hypersecretion or hyposecretion. In the former case the amount of augmentation or inhibition may be greater than the normal; in the latter case the amount of augmentation or inhibition will be less than the normal.

Various older pathological conceptions are now expressed in terms of the modern "internal secretion." The "consensus partium" of the early writers may be regarded as the prime function of the internal secretions. The "formative stimuli" controlling the "vegetative processes" of the body and the "sympathetic" relationships between different parts of the organism are now frequently regarded as depending upon the integrity of the ductless glands or "correlative organs."

An interesting pathological development may be mentioned in this place. Not only in various forms of physiological hypertrophy are we to suppose there is a hypersecretion of a ductless gland, but the same may happen in definite pathological overgrowth; so that it is even believed that in tumours of the internally secreting organs—thyroid, pituitary, pancreas, adrenal—there may be actually a hypersecretion—that is to say, that the tumour cells may secrete in a specific manner.

Some evidence has been put forward for the existence of what is described as "endocrinopathic inheritance," and the relation of such to the Mendelian theory has been considered. But there is not sufficient evidence before us to lead to any very definite conclusions.

There is a gradually increasing tendency to attribute many cases of mental disease and many kinds of neuroses to changes in the ductless glands. Certain writers have attached considerable importance to a relation between endocrine disturbances and the dental apparatus.

It must be confessed that we do not know the functions of any one of the ductless glands in the same definite way in which we know the functions of, for example, the lungs or the pancreas. Owing to the lack of boundaries and the absence of precise exploration in many regions, the territory of internal secretion has been invaded by some irresponsible exploiters. The time has arrived for us to take our bearings and ascertain our precise position with regard to the subject. In doing this, every effort will be made to avoid dogmatism, even at the risk

of losing, or hesitating to accept, some tempting and plausible theories.

In the following pages, after a chapter upon the definition and limitation of the term "internal secretion," it will be desirable to treat first of the general methods of investigation of the subject of internal secretion and the validity of the conclusions which may be drawn from results obtained by such methods. Afterwards the internal secretion of glands which have also an external secretion will be dealt with. These are the liver, the pancreas, the kidney, the intestinal glands, and the gastric glands. Following these, the internal secretion of the testis and ovary (with its corpus luteum [1]) will be described. Then will follow in due order treatment of the function of the "ductless glands"—namely, the adrenal body, consisting of "cortex" and "medulla"; the thyroid body; the parathyroid bodies; the pituitary body, consisting of the "infundibular" or "nervous" portion and the "glandular" portion; the thymus gland; and the pineal body.

Finally will be found a chapter dealing with the relationships which exist between the various internally secreting organs.

[1] The corpus luteum may be looked upon as a "ductless gland," but it will obviously be convenient to treat of it along with the ovary (see p. 75).

CHAPTER II

DEFINITION AND LIMITATION OF THE TERM "INTERNAL SECRETION"

It is obvious at the outset that the term "internal secretion" ought to be employed in such a way that it corresponds as far as possible to the term "external secretion," or secretion by means of ducts. Secretion, as we have seen, is the preparation and setting free of certain substances, the raw material for which is supplied by the circulating blood. Such secretion is the function of certain specially differentiated cells—the secretory cells.

It has already been mentioned that several authors, relying upon the fact that the different organs and tissues of the body have different functions, and therefore pour out into the blood different metabolic products, have insisted that all these have an internal secretion, and that this secretion is in each case a specific one. But this, as pointed out by Kohn, is simply a misuse of the term "secretion." Just as we have certain tissues—namely muscle and nerve—highly specialized and set apart for the functions of motility and conduction of irritability, so we have certain other tissues also highly differentiated and set apart for the purposes of secretion, and it is only to these that we can with propriety ascribe the function. Such are secretory cells and their accumulations, called "glands." The secretory cells are in their origin and in their character *epithelial. Secretory cells are highly specialized epithelial cells.* It is not necessary to insist on this criterion in the case of externally secreting glands, because here it is generally recognized; but it is just as important in regard to internal secretion if the term is to be defined with anything approaching accuracy. The morphological sign of special differentiation in gland cells is the presence of granules which undergo periodical changes in number and position, according

to the stage of activity of the gland. It is not, perhaps, possible to insist on the recognition of granules as definite as those in the pancreatic cells before we admit a structure into the category of internally secreting glands, but *it is essential that the constituent cells should have the general character of glandular—i.e., secretory—cells.* This is in some instances not altogether an easy matter to determine, and, as we shall see later on, there is still some discussion as to whether such a tissue as the *chromaphil* may reasonably be supposed to have a secretory function. That a discussion of this kind should arise in connection with a structure generally supposed to be internally secretory shows how little we know about the actual act of secretion in such a case (see p. 216 *et ff.*).

We conclude, then, that secretion (internal or external) represents a highly specialized grade of metabolic activity, and should be distinguished as rigorously from general metabolism as the contraction of muscle from general motility (Kohn).

Kohn gives a very excellent illustration of the two processes, external secretion and internal secretion. The manufacture of the bile and its conveyance into the duodenum is a secretion in the ordinary sense of the word—an "external" secretion. When we obstruct the bile ducts, the secretion goes on just the same; but now the bile is conducted into the blood-stream, and we get an "internal secretion" of bile. This shows that the products of secretion can, under certain circumstances, pass into the circulation. And we can be tolerably certain that this process can in some tissues occur normally. As we have seen, it is sometimes difficult to decide whether a given tissue is glandular or not, and therefore whether we ought to ascribe to it a secretory function. Thus, Kohn admits the "cortex" only of the adrenal among the glands, while he insists that the "medulla" consists of "chromaphil cells," which are not secretory, not epithelial, and therefore cannot secrete. This point will be referred to later and more fully under the head of the adrenal body (see p. 216 *et ff.*). It may be well, however, to remark in passing that it is from the medulla, and not the cortex, that the active principle is obtained.

We are now in a position to define internal secretion. *The process consists in the preparation and setting free of certain*

substances of physiological utility (the raw materials for which are supplied by the circulating blood), by certain cells of a glandular type ; the substances set free are not passed out on to a free surface, but into the blood-stream.

According to this definition, the products of ordinary metabolism, and even the special products of metabolism arising in such kinds of highly specialized tissues as muscle and nerve, are excluded from the internal secretions.

We have seen that externally secreting glands sometimes manufacture and pour out substances which are waste products, and are no longer of any use in the economy. These are "excretions." It is possible that some of the substances elaborated by the internally secreting glands may also have to be placed in the category of "excretions." They would then be "internal excretions" (see p. 38).

The terms "ductless gland" and "Blutgefässdrüse" were originally applied to a very varied group of structures, including the thyroids and parathyroids, the adrenal bodies, the thymus gland, the pituitary body, the spleen, and the lymphatic glands. But some of these—the spleen and the lymphatic glands—have not a "glandular" structure ; that is to say, they do not consist of epithelial "secreting" cells, and belong to quite a different category of organs, namely, the "hæmolymph" series. The structures usually included at the present time under the title of "ductless glands" are the thyroid gland ; the parathyroid glands ; the adrenal body, consisting of "cortex" and "medulla" ; chromaphil cells and bodies in different regions ; the pituitary body, consisting of the "infundibular" or "nervous" and the "glandular" portion ; the thymus gland ; and the corpus luteum.[1] The thymus originates as an epithelial structure, but subsequently appears to become largely converted into a lymphoid organ.[2] Its morphological characters are therefore unique.

It is believed that these "ductless glands" manufacture and pour, directly or indirectly, into the blood-stream some substance or substances which are of service in the economy, either by supplying a need or by destroying other substances which are needless or positively harmful. This last function

[1] It is possible that we may have to add to the list the "Glandula insularis cervicalis" of N. Pende.

[2] See, however, discussion on p. 329.

—that of "Entgiftung," an "antitoxic" function—is frequently ascribed to the thyroid, though in this, as in other cases, the two conceptions are not necessarily antagonistic. We can readily imagine that a gland may manufacture a definite internal secretion whose active principle may be competent to destroy poisonous products in the blood-stream or in some part of the body.

It is, perhaps, desirable to point out at this stage that the term "internal secretion" has been used too generally and too confidently in many cases. Our knowledge of internal secretion is not to be compared in accuracy and definiteness with our knowledge of "external" or ordinary glandular secretion. Thus, in the case of the submaxillary glands, we can observe the various conditions, loaded or unloaded, of the gland cells. We can watch the flow of the secretion, and regulate it by stimulation of nerves. We can note changes in the volume and blood-supply of the gland concomitantly with the act of secretion. Finally, we can recognize an "enzyme" in the fluid secreted, and are familiar with its chemical action on the food as a process of digestion. Very different is the case, for example, of the medulla of the adrenal body and of the chromaphil tissues generally. Here comparatively little is known of changes in the cells indicative of the act of secretion,[1] and the very fact that any secretion is poured into the blood-stream can only be shown, if shown at all, by laborious and indirect methods. It must be confessed, as a matter of fact, that some of our conceptions in regard to internal secretion are worthy to rank little higher than plausible hypotheses.

But a typical gland having a duct and performing "external secretion" may possess also, according to modern views, the function of "internal secretion." This applies to the liver, the pancreas, the kidney, as well as the intestinal and gastric glands. The liver has, besides the formation of the bile and the glycogenic function (which, owing to its highly special character, is usually not treated along with the internal secretions), the still further duty to render innocuous the end-products of protein metabolism. One of these end-products is ammonia; this is converted in the liver into urea. So that the distinctly poisonous ammonia is transformed in the liver into the com-

[1] See, however, pp. 235, 237.

paratively harmless urea. This is an example of what Biedl calls "*negative internal secretion.*" Since the process is a stage in the elimination of waste material, it might be called "*internal excretion*" (*vide supra*, p. 38).

Recently discovered and extremely interesting examples of internal secretion are furnished by the mechanisms of pancreatic and gastric secretions (*vide infra*, pp. 59 and 65).

There is considerable reason for ascribing an internally secreting function to the testis and to the ovary (*vide infra*, pp. 66 and 75). Though these are not glands in the usual acceptation of the term, yet many of their constituent cells are of the "glandular," "secretory" type.

Lane-Claypon and Starling reported that injections of extract of fœtus into a virgin rabbit causes growth of the mammary glands. Starling suggested the name "Hormone" (from ὁρμάω = I excite or arouse) for these various substances which act as chemical messengers, and the name has in recent years become generally adopted. Foa finds that injection of extract of fœtal calf causes some mammary growth in rabbits. It is concluded, therefore, that the effects described by Lane-Claypon and Starling are not specific for only one kind of animal.

Heape points out that it is well known that virgin animals sometimes produce milk. So that it seems clear that the beginning of the development of the gland dates from some point of time prior to or during pro-œstrum or œstrus, and occurs normally quite apart from pregnancy, and that since the full functional development of the gland may be experienced by virgin animals, this must occur without any stimulus from a fœtus. Heape believes that the source of the stimulus which excites the development of the mammary glands is to be found in what he calls "gonadin," secreted by the ovary at that time, if not in the "generative ferment," which, he holds, governs the activity of the generative glands.

There is now some considerable evidence that the stimulus to growth of the mammary gland arises from the corpus luteum. This will be referred to again and more fully under the head of "The Internal Secretion of the Ovary and the Corpus Luteum" (*vide infra*, Chapter IX., Sect. C., p. 75).

Arguing from the mammary gland experiments, and from those upon the mechanism of pancreatic secretion (*vide infra*,

p. 59) performed in conjunction with Bayliss, Starling has made some interesting generalizations upon this type of mechanism. He points out that in the normal life of the higher animals, looked at as a series of reactions to environmental change, the nervous system plays such a predominant part that we are in danger of overlooking more primitive means of co-ordination between different parts of the body. Starling further points out that in the lowest animals, before the appearance of a central nervous system, it is by chemical means that co-adaptation of function is achieved. As examples he mentions the movement of phagocytic cells towards an irritant, the chase for food, the escape from noxious environment, or the approach of sexual cells. In these cases the mechanism is chemotaxis. The process of action of these stimuli must be slow, and the development of a blood-circulation is necessary in order to quicken it. But before this development occurs, the need for quick reactions has determined the setting apart of special reactive cells; we see, in fact, the rudiments of the nervous system. The whole history of the evolution of man and the higher animals centres about this nervous system.

But in some cases still, where there is no necessity for a specially rapid reaction, as, for example, in the adaptation of the activities of the digestive glands to the presence of food in the alimentary canal, one might expect to find, as Bayliss and Starling actually found, that chemical means of stimulation are employed. Among the various hormones Starling enumerates the gastric and pancreatic hormones, as well as similar bodies which determine the secretory activity both of the liver and the intestinal glands, adrenin, thyroiodin, and the substance secreted by the fœtus during pregnancy. He prophesies that with increasing knowledge the list of these messenger substances will be largely extended, he points out that they are comparable in many respects to the alkaloids, and he intimates that the practice of drugging would therefore seem to be not an unnatural device of man, but the normal method by which a number of the ordinary physiological processes of the organism are carried out.

How far this attitude may be justified by future discoveries must at present remain doubtful, but it certainly represents the view of a large number of modern workers upon the subject of internal secretion. The nervous system is no longer the

only controlling influence to be reckoned with in explaining the bodily functions, and especially is this the ease with the co-ordination and interactions of many of the chief functions of the body. It is even possible that the nervous system itself may be controlled by chemical stimuli.

Leyton has performed some experiments to test the hormone theory of the causation of new growths. The work of Starling and Claypon upon the internal secretion of the fœtus in relation to the mammary gland suggested that perversion of internal secretion might have some relation to the formation of new growths. Such a hypothesis presupposes the existence within the organism of separate substances which stimulate the normal growth and repair of the several organs and tissues, and that each substance is secreted either by its own special organ, or by another organ or tissue. Under the former supposition, so the authors imagine, malignant growth of such tissue would be very unlikely. Under the latter the result might be brought about either by hypersecretion of the substance or by insufficient absorption thereof, whereby in either case the still absorbing tissues would receive an excess. Given an excess of hormone in the organism, together with a lesion or irritation of the tissue complementary to the hormone, unlimited growth might result. It is further conceivable that a real hypersecretion acting on otherwise normal tissue might lead to the formation of a quickly increasing growth, while the relative hypersecretion resulting from diminished absorption from an atrophied senile membrane might account for slow-growing tumours.

The author inoculated previously refractory rats with pieces of glandular organs from known susceptible animals, along with sarcoma. The results in two experiments seemed to show that parotid gland is able to assist sarcoma growth in rats otherwise insusceptible. He further excised the parotid along with inoculation with sarcoma to see if the growth of the tumour was inhibited. The results were not very definite.

Ehrlich thinks that there may be substances circulating in the organism which may stimulate the body cells to resist the athreptic influence of cancer cells. Askanazy believes that certain hyperplasias in the genital organs subsequently to the formation of tumours in the ovary, testis, or pineal body, may

be due to the influence of embryonic tissue formed by the tumour.

The object of the present chapter has been to define as accurately as possible what we mean by internal secretion. The point of greatest importance is to limit our conception of internal secretion so as to include only those processes which are comparable to ordinary or external secretion. We must only allow of the hypothesis of internal secretion in cells which are of a glandular type, and we must diligently search for all signs of cellular activity indicative of secretion. We must further strive to study the process of secretion itself, to discover the products of secretion, to trace them out into the blood-stream, to follow them to their place of activity, and to find their ultimate destination.

In the next chapter we shall study some of the methods of such investigations.

CHAPTER III

GENERAL METHODS OF INVESTIGATION AND THE VALUE OF THE RESULTS WHICH MAY BE OBTAINED BY SUCH METHODS

In the investigation of a subject of such wide physiological import as internal secretion, it is natural that all methods employed in general physiological research should be utilized as occasion demands. The usual methods of experimental physiology, recording devices, and all the appurtenances belonging to the graphic method, are in regular requisition. Physiological chemistry is no longer a mere handmaiden, but is rapidly becoming mistress of the situation. No attempt will be made to pass in review all these details of scientific biological technique. A few of the more important methods which have been of especial service in the development of the subject of internal secretion will be briefly referred to, and an opportunity will at the same time be seized to deal with a few side issues which could not conveniently be treated in any other chapter.

The subject of internal secretion is, of course, a physiological one, but we shall again and again have occasion to make reference to *pathological* methods and pathological data. This is perhaps more emphatically the case than in any other chapter in physiology, because such a large proportion of our knowledge of internal secretion is derived from the realm of pathology, not only from *human pathology*, but also from *experimental pathology*, the result of experiments upon animals.

The fact discovered by Addison in 1855 that the symptoms of what is now known as Addison's disease are due to a lesion of the adrenal bodies is still one of the most important pieces of information we possess about these structures. The association of defective thyroid development or atrophy with cretinoid and myxœdematous conditions is still the sheet anchor of our

knowledge of the thyroid apparatus. The same may be said of the pituitary body and acromegaly, and doubtful as may be the connection between enlarged thymus and sudden death in infants, yet this is almost the only allegation which points to the organ having any definite function.

Experimental pathology in the form of *extirpation experiments* has been largely employed in the attempt to elucidate the functions of the glands with an internal secretion. The method has undoubtedly brought to light many important new facts. It has revealed, for example, the fact that certain of these glands, such as the adrenal and the pituitary, are essential for life, and that removal of the thyroid apparatus entails in most animals very serious results. It has taught us, further, that extirpation of the thymus is without obvious effects. But the results obtained by different observers have often been very contradictory, and the method of complete extirpation has several drawbacks. In the first place the technical difficulties are always very considerable, and are often wellnigh insurmountable. This applies especially to the pituitary body, though modern surgical skill seems at last to have triumphed (see p. 361). It is very frequently impossible to remove just the organ one wishes to remove without doing considerable damage to other tissues. Thus the extirpation of the adrenal bodies and the thyroids must always involve considerable injury to nervous structures and bloodvessels. This consideration must largely account for the contradictory results obtained by different observers. The difficulty of removing the parathyroids without considerable injury to the thyroids can scarcely be overcome, and the successful removal of the pituitary cannot have been performed by more than a very few observers.

Again, we must remember that complete removal of an organ, even if successful from a surgical standpoint, is, owing to its suddenness, an event which can never happen in nature, and can never happen in pathology, and we must be cautious in interpreting the results. The method, however, under modern surgical conditions, is capable of fruitful results, for animals do not appear to suffer to any considerable degree from surgical shock.

Extirpation experiments performed in a series of steps at successive operations are more valuable than when the whole

of an organ (or both organs in the case of bilateral structures) is removed at once. Better still and more fruitful of results are operations in which the organs are crushed, damaged, or infected artificially with the germs of disease, or inoculated with toxins, or partially destroyed by chemical poisons, or in which the blood-supply is interfered with to a more or less complete degree.

Further, extirpation experiments, as usually performed, are only likely to give us useful information in cases where the organ or tissue extirpated normally provides an internal secretion which is needful for the body as a whole. If we remove the submaxillary glands, for example, we find that the animal is apparently unaffected, and the same applies to the mammary and gastric glands. But we are not justified in concluding from these experiments that the glands in question have no internal secretion, but merely that if there be such a secretion, it cannot be regarded as essential to the body as a whole. As a matter of fact, it is now believed that the gastric mucous membrane secretes a specific hormone (*vide infra*, p. 65), and the same has been alleged to be the case with the salivary glands.

Proceedings of a reverse character, such as *grafting*, *feeding*, and *subcutaneous and intravenous injections*, have also been extensively employed in the search for the functions of the ductless and other glands supposed to possess an internal secretion. Experiments in grafting have been chiefly carried out in connection with the thyroid and parathyroid glands, and the reproductive organs. Some work in the same direction has also been done with the adrenals. The object of these experiments has been to replace the extirpated tissue by freshly implanted tissue of the same kind, either in the original situation or in some other part of the body. The earlier attempts were not very successful, and the effects were of a temporary character. The graft became absorbed, and so the final result was no more than that of the administration of a certain dose of the substance of the gland. Some recent experiments, however, have been more successful, and have yielded interesting and important results. An account of these grafting experiments will be given in their appropriate place under the heads of Thyroid, Adrenal, and Reproductive Organs.

Feeding with fresh tissues, or with tissue extracts prepared in various ways, has been very extensively employed. The therapeutic method called "opotherapy" is based upon the principle that the active substance, the "hormone," or the "internal secretion," is absorbed unaltered into the circulation. This is apparently a matter for discussion in some cases, as, for example, in the case of the adrenals (*vide infra*, p. 211). On the other hand, feeding with thyroid glands or thyroid extracts (or even with the so-called active principle, iodothyrin or thyroiodin or thyroxin [Kendall]) has proved a most valuable mode of treatment in cases of cretinism and of myxœdema, and has, besides, been used by physiologists for experimental purposes. But our knowledge of the functions and internal secretions of most of the glands, and especially of their true and intimate relationships to morbid processes and pathological conditions, is still so limited and inexact that it can hardly be expected to furnish guidance in treatment. More especially is this true in regard to the pituitary body, the thymus, and even the pancreas. Among the tissues which have been considered from the standpoint of *opotherapy* or *organotherapy* are, in addition to the thyroid apparatus and the adrenals, the glands of the alimentary tract, the ovary, the testis, the pituitary body, the thymus, the spleen, the bone-marrow, the lymphatic glands, muscle, nerve, and the placenta.

In feeding experiments the effects produced upon metabolism have been carefully studied in many cases. Thus the addition of thyroid substance to the normal dietary of growing rats causes a great increase of food consumption, with alteration of growth and retention of nitrogen in the body. At the same time the nitrogenous metabolism is greatly increased.

Gudernatsch has carried out a very interesting series of experiments showing that certain mammalian ductless glands, when given as food, can exert a decided influence on the growth and differentiation of amphibian embryos, the thyroid stimulates differentiation, but it lacks the power to cause growth. The thymus and spleen stimulate growth, but are wanting in power to excite differentiation.

A word of caution is necessary in respect to the mode of preparation of commercial gland substances. In order to obtain a clean, easily manipulated product, it is usual to remove all fatty matters before desiccation. It is possible,

especially in the case of the adrenal cortex, that some useful principles may thus be removed (see under Adrenal Bodies, p. 203).

Subcutaneous injections of extracts (either fresh or after various modes of extraction and preparation) was the method which first aroused modern interest in the subject of internal secretion. The work of Brown-Séquard in 1889, upon testicular extracts was, perhaps, open to some criticism, but it served to stimulate research in various directions, and led directly or indirectly to very valuable results. Subcutaneous or *intraperitoneal* injection of all other tissues and glands has since been carried out, and the results will be referred to in their proper place. By far the most striking are those obtained by the injection of extracts of the adrenal bodies (*vide infra*, p. 158).

Hypodermic injection of the non-coagulable portion of aqueous extracts of thyroid, parathyroid, thymus, spleen, and liver increases both gastric secretion and the movements of the stomach, while those prepared from the pituitary body and the adrenal inhibit the flow. Pancreatic extract increases the flow of gastric juice. The same kind of extract made from liver causes a marked flow of pancreatic juice. Extracts of thyroid and thymus act less powerfully in the same direction, while those of the pituitary, the parathyroid, spleen, and pancreas are inert. Adrenal extract inhibits the flow. There is not sufficient evidence to warrant us in regarding these effects as manifestations of internal secretion.

Intravenous injection does not appear to have been much used in the study of internal secretions until the publication by Oliver and Schäfer of the extraordinary effects upon the heart and circulation produced by the injection of adrenal extracts, or in more modern phraseology, by extracts made from the chromaphil tissue included in the adrenal (see p. 165 and Figs. 16, 36, 39–43). Since that time, however, the method has been used perhaps to a greater extent than any other. Numerous observers have tested the effects of every imaginable organ and tissue in the hope of finding some remarkable substance in the extracts comparable in its effects with adrenin from chromaphil tissues. Briefly, the results have been as follows. One other tissue besides the chromaphil—namely, the nervous portion of the pituitary—has been found

to contain a pressor substance. All other organs and tissues, but especially nervous tissues, contain a depressor substance, or depressor substances (see Figs. 1–8).

The subject of intravenous injection of tissue extracts has played such a large part in connection with internal secretion that it must be dealt with in some detail. Considerable *naïveté* has been displayed by many observers, both as to details of method and as to the interpretation of the results obtained. Thus, for example, it has too often been assumed that a slight rise or fall of the blood-pressure obtained after injection of a fluid into the circulation is in reality due to some specific action of the extract, and not due, as it very likely is, to its effects *qua* fluid, or to its temperature, or to the rate of injection, or to some other adventitious circumstance. Again, it has been rashly concluded in many cases that because an extract of a certain tissue or organ produces a certain effect, for example, on the blood-pressure, that this is evidence of an internal secretion on the part of the tissue or organ in question. This unjustifiable attitude is being continually maintained. Thus, Livon divides the glands of the body into two groups, "hypertensive" and "hypotensive," according as their extracts when injected into the circulation of an animal cause a rise or a fall of the blood-pressure. The adrenals, the pituitary, the spleen, the kidney,[1] and the parotid, are placed in the former group; the liver, lung, pancreas, thymus, ovary, and testis in the latter.

As we have seen, the remarkable discovery of Oliver and Schäfer stimulated numerous observations upon the special physiological effects of extracts made from different organs and tissues. These authors noted, in addition to the effects of adrenal extracts, that pituitary preparations also produce a rise of blood-pressure. And we may state at the present time, with some degree of certainty, that these are the only two tissues in the body an extract of which produces *pressor* effects.

Professor Schäfer also, working in conjunction with the present writer, found that a *depressor* substance is also present in pituitary extracts, and noted "a certain similarity of physio-

[1] It is doubtful in any case whether the spleen and kidney would be included in the pressor group. (In regard to the kidney, see p. 52.)

logical action between nervous matter and the infundibular part of the pituitary." A striking result in some of our experiments was the causation of very extensive irregularities in the blood-pressure curve after injection of brain extracts. Schäfer and Moore had previously noted a lowering of blood-pressure on injection of brain extracts, but they did not lay any stress on the observation. Professor Osborne and the author worked out fully the effects of nervous-tissue extracts, and found that extracts made from all parts of the nervous system produce a marked temporary fall of arterial blood-pressure, which can be obtained after section of both vagi and after administration of sufficient atropin to abolish vagus action (see Figs. 1 to 5). We came to the conclusion (contrary to that of Mott and Halliburton) that, although choline was present in small amounts in the extracts, the depressor effect was not due to the presence of that substance. The reason for this view was that, whereas after the administration of atropin to an animal, choline always produces a rise of blood-pressure, these extracts, on the contrary, always produced a fall (see Figs. 3–5).

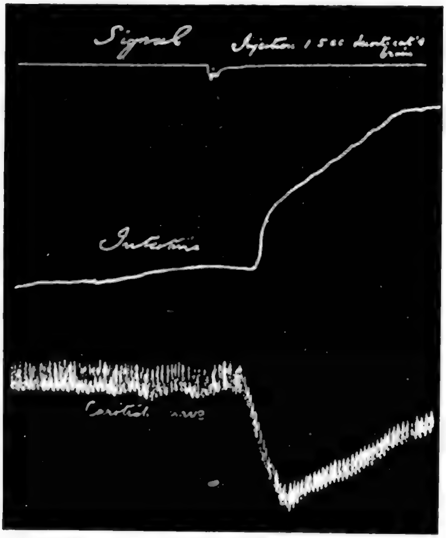


Fig. 1.—Dog. A.C.E., morphine, curare, artificial respiration. Loop of intestine in air plethysmograph. Injection of 1·5 c.c. decoction cat's brain (Osborne and Vincent).

Figs. 1 and 2 show the effects of extracts of brain and spinal cord upon the blood-pressure, the volume of the intestinal wall, the volume of the hind-limb, and upon the contraction of the auricle and the ventricle of the heart.

Figs. 3, 4, and 5 show the difference in action between nervous-tissue extracts and choline in an atropinized animal.

Vincent and Sheen found that a depressor substance can be

extracted, not only from nervous tissues, but also from all kinds of muscular tissue, kidney, liver, spleen, testis, pancreas, ovary, and lung. They note, also, that other observers have extracted a depressor substance from thyroid, thymus, adrenal, and pituitary body.

Figs. 6 and 7 show the effect of injection of extracts of muscle. Fig. 8 shows the effect of brain extract for the purpose of comparison.

By this time it had become tolerably clear to the present writer that all animal tissues impart to watery or saline extracts a substance or substances which, when injected into the circulation of a living animal, affect the arterial blood-pressure. The effect produced by these substances is depressor, with the exception of the medulla of the adrenal ["paraganglion suprarenale" (Kohn)], other groups of chromaphil cells, and the infundibular portion of the pituitary body. It had also been rendered probable that these depressor effects of an extract are not to be regarded as an indication of an internal secretion on the part of the tissues in question. This seems now to be generally recognized, and the view is adopted in the majority of textbooks.

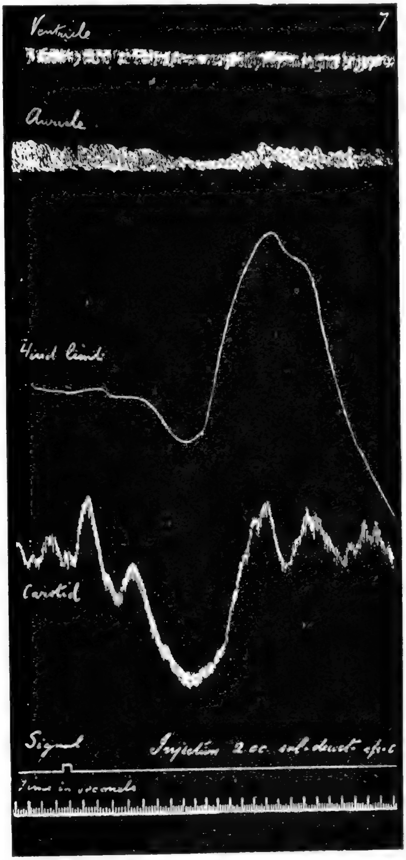


Fig. 2.—Dog. A.C.E., morphine, curare, artificial respiration. Hind-limb plethysmograph. Hooks in auricle and ventricle. Injection of 2 c.c. saline decoction spinal cord (Osborne and Vincent).

It is naturally of some interest and importance to ascertain

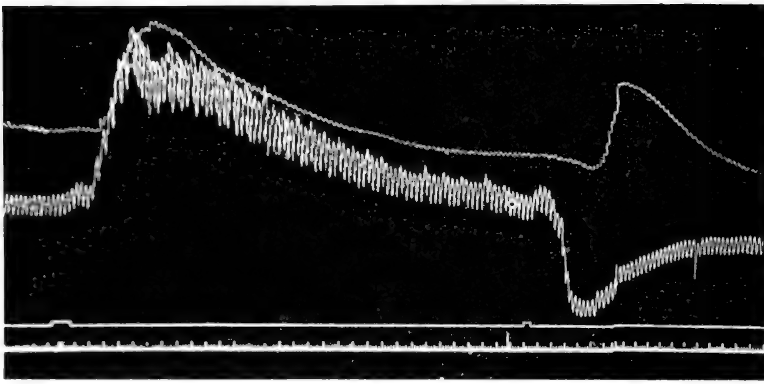


FIG. 3.—Dog. A.C.E., morphine, curare, artificial respiration, atropin. The first injection = choline. The second = saline decoction of brain. (Osborne and Vincent).

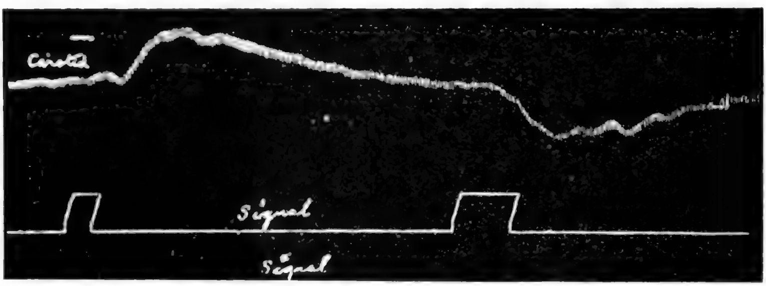


FIG. 4.—Cat. A.C.E., morphine, atropin. First injection = 1 c.c. of 0·2 per cent. choline. The second = 1 c.c. brain decoction (Osborne and Vincent).

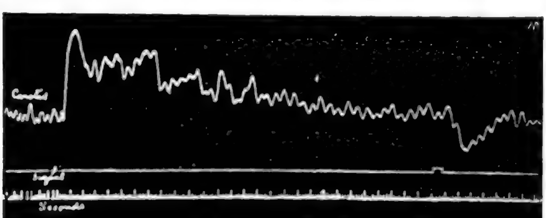


FIG. 5.—Rabbit. A.C.E., morphine, atropin. First injection = choline. The second = brain decoction (Osborne and Vincent).

as far as possible how far the active substances are identical in different tissues. The present writer, working in conjunction with Dr. Cramer, found that there are two groups of substances in watery extracts of nervous tissues, which, when injected into the veins of an animal, lower the blood-pressure. Both of these groups

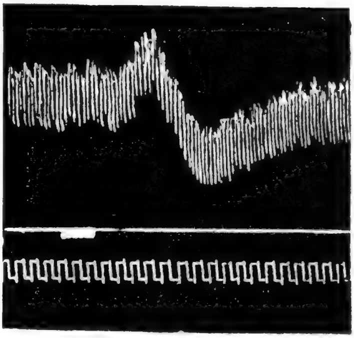


Fig. 6.—Dog. A.C.E., morphine. Injection of 5 c.c. "protein" extract of striped muscle (Vincent and Sheen).

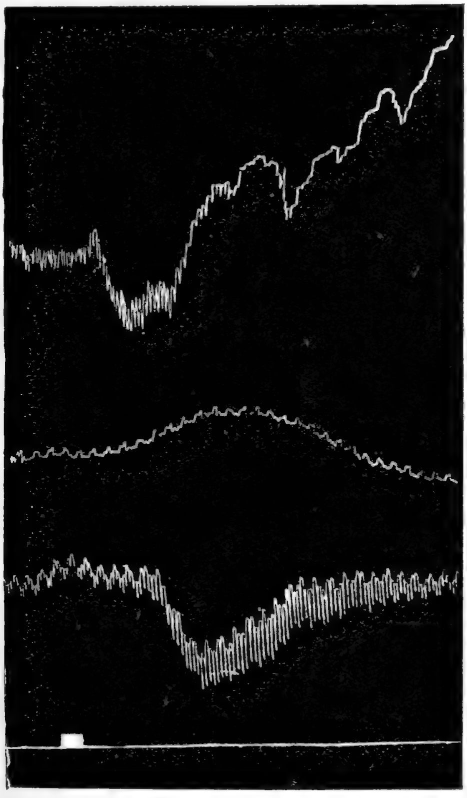


Fig. 7.—Dog. A.C.E., morphine, curare, artificial respiration. Upper curve = intestine; middle curve = limb; lower curve = carotid blood-pressure. Injection of 5 c.c. saline decoction striped muscle of rabbit (Vincent and Sheen).

are soluble in water. One group is easily soluble in absolute alcohol, and the other scarcely soluble in this fluid. The alcoholic solution contains two depressor substances; one of them has its effect abolished by atropin, the other has not. The latter is the more powerful, but rather the less soluble in alcohol. The alcoholic solution gives an abundant precipitate with platinum chloride. Only a small part of this is readily soluble in water, and on purifying gives octahedra and prismatic crystals. The greater part of the precipitate

consists of the platinum chlorides of potassium and ammonium. The octahedra are the ammonium salt. Since the prisms have a percentage of 32·8—*i.e.*, 1·2 per cent. higher than would correspond to the platinum salt of choline—and since the free base has a physiological action slightly different from that of choline, it would follow that the base is not choline, but a choline-like body, perhaps a di-choline anhydride.

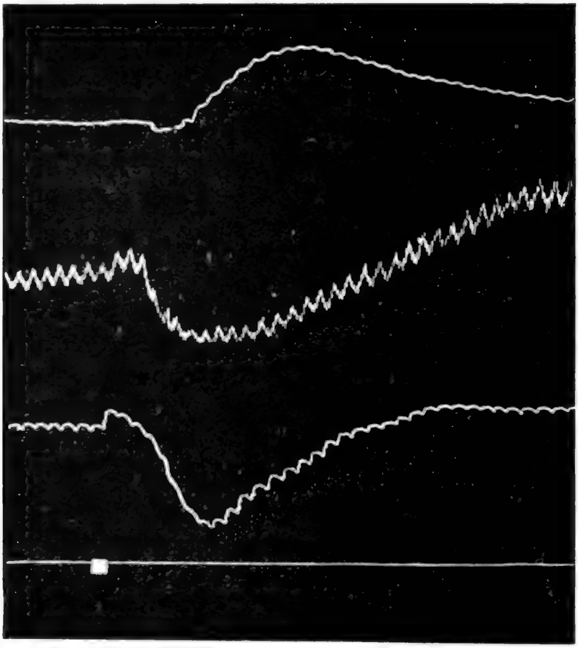


FIG. 8.—Dog. A.C.E., morphine, curare, artificial respiration. Upper curve = limb volume: middle curve = intestine; lower curve = carotid blood-pressure. Effect of injection of 5 c.c. alcoholic extract of rabbit's brain (Vincent and Sheen).

Apart from this choline-like body, we did not find any choline as such in brain extracts, and we fully confirmed the view of Osborne and Vincent, and Vincent and Sheen, that the depressor effects of nervous-tissue extracts are not due to choline. We stated that the chemical and physiological tests recommended for this substance in pathological blood cannot be relied upon; indeed, normal blood gives both the octahedral crystals and the depressor effect on the blood-pressure,

In regard to the chemical nature of the depressor substance in tissue extracts, nothing positive has yet been discovered. It has been suggested that it may be histamine (β—Iminazolylethylamine) but more recent investigations have rendered this hypothesis untenable.

It is doubtful whether the presence of these depressor substances in tissue extracts has any physiological significance. Recent literature supplies many contributions from authors who become impressed by the fact that some organ (such as a lymphatic gland) yields a depressor substance to extracts, and therefrom rashly assume that it is the function or one of the functions of the organ in question to pour out this depressor substance as an internal secretion to minister to the needs of the economy.

Abelous and Bardier find in normal urine a substance which raises the blood-pressure. This substance they call "urohypertensin," but it is satisfactory that so far there has been no suggestion that this is any kind of "hormone" or evidence of an "internal secretion."

The physiological activity of the amines which are formed when carbon dioxide is split off from amino-acids, as, for example, by putrefaction, ought perhaps to be referred to here. Abelous first noted the presence of pressor principles in putrid meat. These have since been identified by Barger and Walpole as isoamylamine, phenyl-ethylamine, and p. hydroxyphenylethylamine.

But, of course, the effects upon the blood-pressure are not the only actions of tissue extracts which have been studied. The influences which such extracts exert upon the heart are studied by recording directly the heart movements either in the body or isolated in the lower vertebrata, and in mammals, and various forms of tonometers and plethysmographs have been employed for registering changes in the volume of the heart. The muscle-nerve preparation may be used to demonstrate the action of the extracts upon muscle and upon nerve. The volume of organs, the rate of flow of secretions, and the movements of muscular tissues, are also observed. In fact, all the modern methods of observing and recording changes in physiological conditions are constantly employed for the study of the action of tissue extracts.

An interesting method of studying the action of animal

extracts on the peripheral vessels was employed by Oliver. The vessels of the frog's mesentery were observed before and after the application of a drop of normal saline (as a control) and of normal saline containing 1 per cent. of the organ dried at 38° C.—the simple saline and the saline extract being exactly of the same temperature (16° C.). Throughout each observation the micrometer scale was kept *in situ* over exactly the same portion of an artery and its companion vein; and when any change of calibre was observed to follow the application of the saline extract its duration and degree were noted until the calibre was restored, and it was accepted as the effect of the extract when it exceeded the normal variations and when it was practically immediate, was invariable, and when it lasted a certain uniform time, and was succeeded by restoration of the calibre. There was not much effect except in the case of adrenal extracts. This constricting effect of adrenal extract on the peripheral vessels may likewise be observed by the unaided eye by setting up inflammation of the conjunctiva in a rabbit (as by touching the eyeball with a glass rod dipped in acetic acid) and then dropping the extract on the injected surface, when the redness quickly vanishes, and remains absent for about half an hour.

But even if, on injection of an extract of an organ, we get several different effects on the organism, it is obvious that we have no right to assume on these grounds alone that the organ yields an "internal secretion." This may be suspected when the extract yields a substance having very special physiological actions, but can be definitely stated only when the organ consists of glandular "secreting" cells which show histological signs of activity (granules, etc.), and when the blood which leaves the organs by its veins can be found to contain the same active principle as the organ itself. To make the evidence for internal secretion complete, it ought to be possible to recognize in the symptoms produced by extirpation of the organ the direct and reasonable effects of absence of the active principle, the internal secretion, and to remove these symptoms by replacing the organ in some other part of the body or by administering the active principle in some form or other.

Isolated organs and tissues are now employed frequently in order to test the effects upon them of extracts of the various organs. Thus a strip of uterine wall or of different portions of

the intestine may be suspended from the short arm of a writing lever in a cylinder containing Locke's fluid at the proper temperature. Then the fluid may be replaced by any other (such as an organ extract) whose action it is desired to record. Various organs yield extracts which will produce distinct effects upon such muscle preparations. Many of these have been shown not to be specific. The more important of them will be referred to again under adrenal bodies, pituitary, etc. This method is one of extreme delicacy, and great care should be taken that proper control experiments are carried out. The preparations are very susceptible to slight changes of temperature, slight accidental mechanical stimuli, and in all probability the rate of change of dosage of the active substance makes a great difference to the result. Distinct effects are reported to be noticed by this method when adrenin in dilutions of 1 : 500 millions is employed.

The electrical response as an index of glandular activity has been employed to study the activity of the thyroid gland. By preliminary experiments with the submaxillary it appeared that the electrical change is a manifestation of the secretory process and not of anything else. The results of these experiments will be described in the chapter on the thyroid (p. 308).

Abel has recently introduced a method which he calls "vividiffusion," which seems likely to be of great service in the study of the internal secretions. An artery or vein is connected by a cannula to an apparatus made of celloidin in the form of tubes immersed in a saline solution, and providing for the return of the blood to the animal's body by another cannula attached to a vein. The tubes and cannulæ are filled with saline solution. This is displaced into the body by the inflow of blood when the circulation in the apparatus is established. The blood leaving the artery flows through a perfectly closed system and returns to the body within a minute or two, while the diffusible substances which it contains can pass out through the walls of the tubes. Coagulation of the blood is prevented by means of hirudin. If, then, the hormones are diffusible substances they may be separated from the circulating blood by this method.

The employment of *cytotoxic sera* as a means of investigating the tissues concerned in internal secretion has so far not yielded

any results of importance. The antibodies obtained are not specific for any particular organ or tissue.

It seems to the present writer that one of the methods which will yield the most valuable results in the near future is the oldest of all—namely, careful study of clinical conditions and a patient investigation of pathological anatomical findings. Now that the microscopical structure and the comparative anatomy has been worked out with some completeness, and the results of extirpation experiments and the action of organ extracts fairly well known, pathologists may return to the problems with a better foundation of knowledge and fresh hopes for future discovery.

CHAPTER IV

THE NATURE, MODE OF ACTION, AND ORIGIN OF HORMONES

HORMONES may conceivably be of two kinds—namely, *augmentary* and *inhibitory*—analogous in their action to the two well-known kinds of nerve fibres. But it would seem probable that the inhibitory is in many cases the only active influence exerted. This may be regarded as a putting on of the brake, while the augmentary influence is simply a case of removing the brake. In other words, the organs have a superabundance of stored energy, and are constantly tending to over-activity. The normal degree of activity is determined by *inhibitory* influences. These influences may be nervous, or, as we have seen, they may be chemical.

But there seem to be some definite examples of *augmentary hormones*, as, for example, secretin and adrenin. The two groups are sometimes called "assimilation" and "dissimilation" hormones.

Sir E. Sharpey Schäfer suggests the name "autocoid substance" instead of "hormone," and restricts the term "hormones" to the excitatory autocoid substances, while those whose actions are inhibitory are called "chalones." Matthews has recently introduced the term "cryptorhetic tissues" as applied to those furnishing an internal secretion. These organs and tissues are also often referred to as "endocrine" or "endocrinous," and the subject as "endocrinology."

Nothing definite can be stated about the origin of hormones in general. In the case of some of the individual hormones, the matter may be discussed in its proper place.

The hormones which have so far been described are secretin, the gastric hormone, the hormones of the liver, pancreas, kidney, testis, ovary, and corpus luteum, as well as adrenin and the active substances of the thyroid apparatus and the pituitary body.

Zuelzer, Dorhn and Marxer (in a series of communications dating from the year 1908) have described the property which extracts of certain tissues (gastric and duodenal mucous membrane, and the spleen) have of exciting intestinal peristalsis. This property they refer to "peristaltic hormone." A substance called "hormonal," said to contain a solution of the hormone, has been recently put upon the market. If used for therapeutic purposes, the peristaltic hormone must be introduced intravenously or intramuscularly. It has been strongly recommended for atonic constipation. The hormone is probably developed in the gastric mucous membrane and stored in the spleen. It is pointed out by Starling that the hormones must not be of such a character as to produce antibodies, that if they are to pass easily through the walls of the blood-vessels, they must have a comparatively low molecular weight, and that they should be susceptible of easy destruction in the fluids of the body. It is said that they are destroyed by ultra-violet rays.

Our knowledge of the chemical nature of the hormones is at present confined to adrenin and possibly to the recently discovered thyroxin of Kendall. (See Chap. XI.)

In 1911 Eppinger and Hess enunciated a complicated theory that not only is the whole sympathetic controlled by adrenin, but that the autonomic fibres other than those of the sympathetic proper are dependent on the beneficent influence of a hypothetical hormone—*autonomin*. This is sometimes called "Hormone X." There are no sound reasons for believing that any such hormone exists.

Gley has recently suggested a classification of endocrine substances based upon their general physiological actions. Substances which regulate chemical processes and functions he calls "*Harmozones*" (ἁρμόζω, I regulate). Under this head he includes the substance which controls the production of sugar, adrenin (in so far as it is concerned in the mobilization of sugar), and antithrombin. Starling's term "hormone" Gley proposes to restrict to specific functional excitants such as secretin, thyroid substance, and adrenin, while he introduces the term "*Parhormones*" to include products of metabolic activity which have a physiological rôle such as carbon dioxide. When we consider how little we know about the internal secretions, we are tempted to regret that the nomenclature

has already become so abstruse and complicated. In the opinion of the present writer the term "internal secretion" is sufficient to satisfy all the working requirements of the subject.

CHAPTER V

THE INTERNAL SECRETION OF THE LIVER

As stated in a preliminary manner above, the liver has, in addition to the formation of the bile, several important metabolic duties. The chief of these, the glycogenic function, has already been alluded to, and although to it was first applied the name "internal secretion," we shall not treat of the subject any further, for the reasons that the process is a highly special one, and that it would occupy too much space to treat of the enormous literature of the subject.

It is possible that some of the ductless glands which are usually supposed to act only on the pancreas may act on the liver by means of the sympathetic nerves.

A word or two ought to be said about the duty of the liver in rendering innocuous the end-products of protein metabolism. There are many facts which point to the significance of the liver in the production of urea. In the dog, when the arterial blood-supply is completely cut off from the organ, the ratio of the urea to the total nitrogen of the urine falls considerably. The liver can manufacture urea not only out of NH_3, but also from other nitrogenous bodies. So far as the production of urea from ammonia compounds is concerned, the process involves an antitoxic action, the distinctly poisonous ammonia being transformed into the comparatively harmless urea. This is what Biedl calls a "negative internal secretion," and what has already been referred to as "internal excretion" (pp. 14, 16). There are, however, probably several sources of urea in the body, and several distinct places of origin.

The liver is stated to be antitoxic also for other poisons, such as strychnine and nicotine, but not for atropine and curare. According to Charrin, the protective action of the liver in

certain intoxications is probably due to its action on the coagulability of the blood.

According to some authors, extracts of the liver are toxic. Mairet and Vires find that injection of a watery extract of rabbit's liver into the veins of another rabbit causes various severe affections of the respiration, heart's action, and the nervous system, and a dose of 60 grammes per kilogramme of body weight is fatal. The efficiency disappears on heating the extract. Of course, these are enormous doses. It is probable that in corresponding doses other animal extracts prepared in the same way would be equally injurious.

Liver extracts have been administered therapeutically in several affections. The value of cod-liver oil has been supposed to be due to its containing some of the internal secretions of the liver. Hepatic opotherapy is recommended in digestive disorders, hepatic insufficiency, hepatic cirrhosis, hæmorrhages due to liver disorders, phlebitis, icterus, hepatic diabetes, gout, anæmia, and tuberculosis. It is in cases of hepatic diabetes that liver extracts might be tried with the best prospects of success, but it cannot be guaranteed that any good results will certainly accrue.

CHAPTER VI

THE INTERNAL SECRETION OF THE PANCREAS

THE most usually quoted example of a gland which has both an internal and an external secretion is the pancreas. A relation between diseases of the pancreas and diabetes has long been suspected, but Minkowski and Mehring first definitely showed that complete removal of the pancreas in the dog, cat, and pig is followed by diabetes having the usual symptoms of that disease in man. That this is caused by the absence of an internal secretion is proved by the facts that it does not occur if the gland be left *in situ* and the duct tied, nor does it occur if a portion of the pancreas be grafted in some situation remote from its normal position (*e.g.*, underneath the skin or in the peritoneum).

It is interesting to note that a dog dying from pancreatic diabetes eats ravenously because of increased intensity of the gastric hunger contractions.

It has been observed that complete pancreatectomy in pregnant bitches near term does not result in diabetes, although there is serious general disturbance.

How the internal secretion of the pancreas normally prevents glycosuria is not clear. We can only say that it exerts some influence upon the carbohydrate metabolism, either by favouring the formation of glycogen in the liver from the glucose taken to it by the portal vein, or by furthering the oxidation of glucose in the tissues generally.

Pflüger confirmed the observation of Marcuse that extirpation of the pancreas in the frog produces the same symptoms as in mammals. He also makes the further statement that extirpation of the duodenum or separation of the duodenum from the pancreas—the blood-supply of the gland being left intact—has the same effect. Pflüger criticizes the ordinary

internal secretion theory of the pancreas, and substitutes for it a theory according to which there exist nerve centres, stimulation of which determine the production of sugar, and other centres of an antagonistic nature determining an internal secretion of the pancreas, which internal secretion hinders the production of sugar. In removing the pancreas these centres are necessarily damaged, and the same happens in extirpation of the duodenum or separation of the duodenum from the pancreas.

Herlitzka, working with frogs, agrees that the ganglia in the wall of the duodenum are necessary for the normal internal secretion of the pancreas, and agrees with the doctrine of Pflüger that the correlation between duodenum and pancreas is due to the action of these ganglia.

Vahlen points out that it is usually believed that there is in the pancreas a material which promotes the destruction of sugar in the organism, and that this unknown substance splits up the sugar in some way and thereby makes oxidation easier. The author referred to has tried to isolate such a substance, with entirely negative results, but he thinks he has obtained a constituent of the pancreas which acts in a purely catalytic manner on the vital destruction of sugar.

Pancreatic extracts exercise an inhibitory influence on the production of lactic acid in surviving muscle.

The Islets of Langerhans

By perhaps the majority of authors the pancreas is considered to consist of two separate and distinct kinds of tissue, the secreting alveoli, and the islets of Langerhans. The question, however, as to the morphology and physiology of the islets of Langerhans needs a little discussion. Modern writers may be divided into two chief groups according to their views as to the morphological significance of the islets. The first of these believe that the islets are essentially of the same embryological and morphological nature as the zymogenous tubules, and are not to be looked upon as, in any sense, organs *sui generis*. The second group of observers regard the structures in question as definite and distinct organs, analogous to the cortex of the adrenal, the epithelial part of the pituitary body, and the parathyroids, and consider that they have no connection

(except a community of embryonic origin) with the secreting tubules of the pancreas.

Some among the first group of writers even consider there may be no difference *in function* between the two structures. Thus Harris and Gow thought that the islets might take part in the external secretion, probably forming one of the ferments. Some authors look upon the islets as exhausted secreting cavities, and believe that after a period of repose they may again take on their secretory function. Others, on the contrary, look upon the islets as exhausted acini which are unable to return to their former state.

In most vertebrates there are no lumina in the islets of Langerhans, but such have been described occasionally in amphibians and reptiles.

Laguesse refuses to admit that the islets are simply exhausted masses of acini, or that they are in their nature simply secreting tubes modified by inanition, and he urges against either of these theories the abundance of the granules of secretion in the islets, the permanent juxtasplenic islet of the Ophidians, and the fact that islets are found in every functional state of the pancreas. The presence of lumina in the islets of reptiles is a strong indication that their origin is from alveoli. The same author, in his numerous contributions on the subject, has laid stress on the anatomical details above referred to, and inclines strongly to the view that the islets of Langerhans are portions of the secreting tubules temporarily modified for the purpose of supplying an internal secretion.

Dale employed a new method for investigation of the subject, using secretin to exhaust the gland. He concluded that the islets of Langerhans are not independent structures, but are formed by certain changes in the cells of the secreting tissue of the pancreas. The change from the secreting to the "islet" condition may be accelerated by the administration of secretin and as a result of inanition.

The authors belonging to the second chief group all believe in the internal-secretion theory of the islets, and, indeed, so convinced are many of them that this is the correct theory, that they do not accept the statements of the first group, who describe changes in the islet in exhaustion and inanition, and the transition forms from one kind of tissue to the other. According to Diamare, the islets are "epithelial bodies" in

Kohn's sense. They are constant and invariable, and are a form of "epithelial body" derived from the pancreas (for he admits, of course, the common embryonic origin of pancreas and islets). The adult islets, in his view, have no relation to the surrounding tissue, except that of contiguity, and he denies that the islets ever possess lumina, even in reptiles. He denies the continuity of the islets with the exocrine gland and all

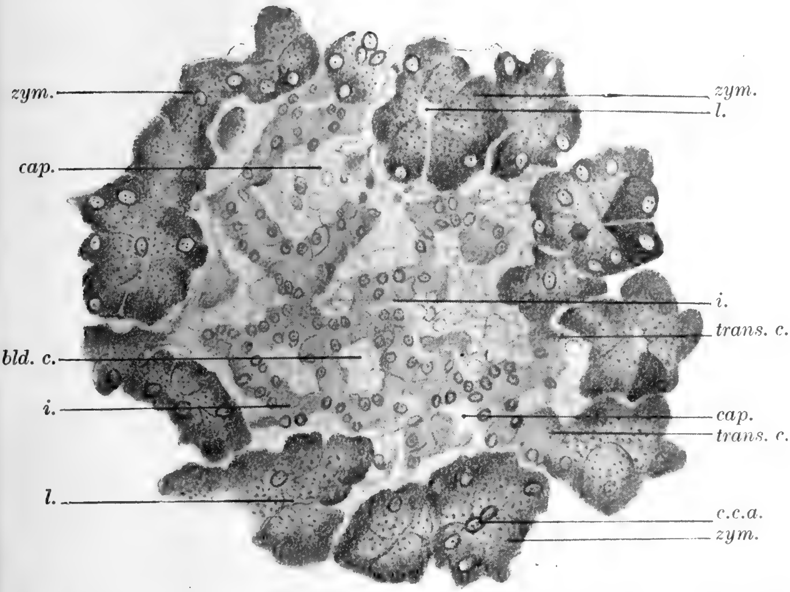


FIG. 9.—Islet of Langerhans, from the splenic end of the pancreas of a normal dog, showing the alveolar form of the islet tissue. The tissue of the islet is seen to consist of solid branching columns of cells, for the most part two deep, separated by wide capillary bloodvessels (Vincent and Thompson). (Drawn by Mrs. F. D. Thompson.)

Lettering common to Figs. 10, 11, and 12.—*bld.c.*, red blood-corpuscles; *c.a.c.*, centro-acinar cells; *cap.*, blood-capillaries; *i.*, islet of Langerhans; *l.*, lumen; *trans.c.*, transitional cells; *zym.*, zymogenous tissue.

forms of physiological variation. Rennie, in his work on the teleostean fishes, describes the fairly constant occurrence of an encapsuled islet ("principal islet") of large size, whose relation to the pancreatic tissue is frequently extremely slight. He considers the islets to be "blood-glands" which have entered into a secondary relation to the pancreas. This author finds no sign of any transitional forms.

The present writer, as the result of investigations carried out in conjunction with Mrs. Thompson, considers that the embryological work of Laguesse and the experimental researches of Dale are confirmed in all essential points.

Fig. 9 represents an islet of Langerhans from the splenic end of the pancreas of a normal dog, showing the "alveolar" form of the islet tissue. The islet is seen to consist of solid, branching columns of cells, for the most part two deep, separated by wide capillary blood vessels. In some places the zymogenous tissue shows transitions towards islet. Fig. 10

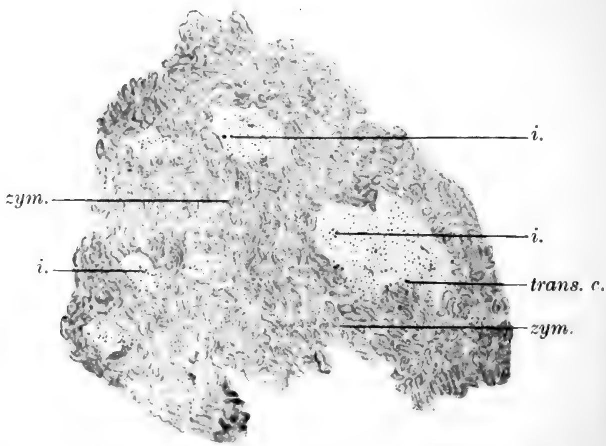


FIG. 10.—From the splenic end of the pancreas of a normal pigeon. The section shows the islets and the zymogenous tissue. Compare this with the next figure (Vincent and Thompson). (Drawn by Mrs. F. D. Thompson.) Lettering same as for Fig. 9.

is a section taken from the splenic end of the pancreas of a normal pigeon. The section shows the islets and the zymogenous tissue. Compare this with Fig. 11, which shows the splenic end of the pancreas of a pigeon after a few days' inanition. The increase in the amount of islet tissue is very striking.

If a pancreas from an animal in inanition is examined, a very remarkable increase in islet tissue is noted[1] (see Figs.

[1] It must be admitted that this does not occur with complete regularity, but probably depends upon the state of nutrition of the animal at the time the inanition is begun.

10 and 11), but if after such a period the animal is restored to its normal state of nutrition, the usual proportion of islet tissue is found. The most obvious explanation of this is that the alveoli are reformed from the islet tissue. There is, however, another possibility—namely, that the islet tissue formed from alveoli, as a result of changed physiological conditions, is not reconverted into secreting tubules, but, having reached the last stage of its career, degenerates and disappears. If this

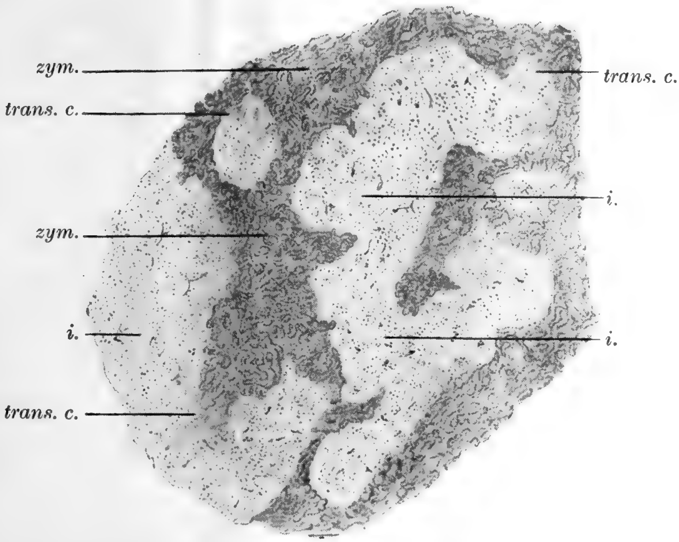


FIG. 11.—Splenic end of the pancreas of a pigeon after a few days' inanition. The increase in the amount of islet tissue is very marked (Vincent and Thompson). *Cf.* with Fig. 10. (Drawn by Mrs. F. D. Thompson.) Lettering same as for Fig. 9.

be the case, we must assume that new alveoli are formed from the existing tubules, and occupy the space recently occupied by islets. On this hypothesis the more solid islets might be regarded as nothing more than worn-out alveoli about to disappear. Of the two possible views here put forward, the present writer is inclined to support the former.

Feeding dogs upon a purely carbohydrate diet also increases the amount of islet tissue, and removal of the spleen from frogs has a similar effect.

Experiments involving ligature of the pancreatic duct have given contradictory results in the hands of various observers. Many writers have alleged that if a portion of the pancreas is separated from the rest of the gland and its duct tied it atrophies and leaves a tissue containing enlarged islets.

Schäfer was the first to suggest that the islets of Langerhans are the part of the pancreatic tissue concerned with carbohydrate metabolism. A number of more recent observers have found in cases of diabetes mellitus that the islets are affected by a hyaline degeneration, atrophy, or inflammatory changes ; but others have been unable to confirm these results. Notwithstanding the conflicting nature of the evidence upon this point, a large number of pathologists have—at any rate, until quite recently—appeared to favour the view that the islets of Langerhans constitute a tissue *sui generis*, whose function it is to control, by means of some kind of internal secretion, the metabolism of sugar in the body.

Diamare has, indeed, put forward some experimental work in support of this definite view as to the function of the islets. He finds that the amylolytic ferment occurs only in the ordinary pancreatic cells, while it is absent in the islets of Langerhans. He states that the islets possess the power of inverting grape-sugar, and is of opinion that these structures are intimately concerned in the economy of glucose in the body. The glycolytic action of the islets *in vitro* is very weak, and he looks upon the tissue as furnishing an endocrine zymoplastic secretion. Hyperglycæmia and diabetes are in this view the result of functional insufficiency of the islets. This observer further records certain modifications occurring in the islets of *Motella tricirrata* as the result of the injection of glucose into the abdominal vein.

As we have seen, the present writer was the first to prove experimentally that the islets of Langerhans actually pass through a structural cycle, corresponding to a cycle of changes in physiological conditions. We were able to provoke experimentally the formation of new islets at the expense of the exocrine parenchyma, and then to induce their disappearance by a new transformation into acini.

Laguesse, working with the pigeon, has been able to confirm our results. He has performed a very large number of experi-

ments, and his results are carefully tabulated. He gives, moreover, a careful account of the anatomy of the pancreas in the pigeon. He states his conclusions as follows: "Chez les animaux soumis à l'inanition pendant quelques jours, le nombre des ilots double presque, pour retomber à son taux normal chez les pigeons renourris." "Nos observations, complêtant et élargissant celles de Swale Vincent et Thompson, nous paraissent fournir une preuve expérimentale très demonstrative du balancement."

The results of recent investigations have not been very concordant. M. Labbé and P. Thaon have reported an increase in amount of islet tissue in guinea-pigs when fed on animal food. This result may possibly be attributed to inanition.

Bensley, as the result of very painstaking work, finds himself unable to agree with Vincent and Thompson. He has used Lane's methods for the study of the cell granules and has adopted the classification into A and B cells, according as the granules are fixed respectively by alcoholic or watery solutions. In order to test the question as to alterations in islet tissue under different conditions, this author employed the neutral red method for staining the islets and for their enumeration. He has taken no account of the size of the islets. He believes that the structures in question are constant and do not change under different physiological conditions.

Von Hansemann confesses that he has been forced to change his opinion as to the significance of the islets of Langerhans. He now regards them as varieties of the parenchyma of the organ and not as separate structures. He finds that in diabetes the changes in the islets correspond exactly to those in the rest of the organ.

Pratt and Murphy have observed that pancreatic tissue implanted in the spleen and separated from its original vascular and nervous connections can live and functionate for months. A small nodule of pancreas composed of acini without demonstrable islets prevented the development of diabetes. This shows that the islets are not the only portions of the pancreas which furnish an internal secretion. Other experiments of the same nature and with similar results have been recorded.

Adami affirms that he has encountered appearances in the human subject which would be difficult to explain, except on the hypothesis that the islands are not separate organs; that they vary in number according to the state of nutrition and activity of the gland, becoming converted into active acini, and *vice versâ*. As Adami justly points out, these observations do not wholly negative the contention that the islands bear some intimate relationship to a certain order of cases of diabetes; they suggest, however, that degenerative changes seen in them are an indication of other changes occurring in the intimately connected pancreatic tissue proper.

Whatever may be subsequently discovered to be the true function of the islets of Langerhans, their intimate anatomical relationship with the zymogenous tubules, the numerous transition forms in all groups of vertebrates, and the transformation of alveolus into islet, and *vice versâ*, all appear to prove conclusively that the islets are not organs *sui generis*, but are an integral part of the pancreatic tissue. As to whether the temporary structural modification of alveolus into islet tissue corresponds to a specialization of function, the evidence is at present inconclusive.

A prolonged discussion of the pathology of glycosuria and speculations as to the precise manner in which the internal secretion of the pancreas normally prevents such a condition, would serve no useful purpose. It is, however, of supreme importance to bear in mind that a certain order of cases of diabetes mellitus are, in all probability, due to insufficiency of the internal secretion of the pancreas. But we must bear in mind the possible influence of disturbances in certain others of the endocrine glands which are concerned with carbohydrate metabolism, as, for example, the adrenal and the thyroid. In disease of the pancreas the limit of assimilation for carbohydrate may be greatly lowered even when spontaneous glycosuria does not occur.

The symptoms of diabetes as observed in the human subject are well known, and need only be referred to briefly. The cases are described as *acute* and *chronic*, the former usually occurring in children, the latter usually in older people. There are *mild* and *severe* cases, and there are the *fat* or *emaciated* cases. Many other subdivisions and classifications have been suggested. Polyuria, thirst, increased appetite, dryness of

the skin, constipation, loss of sexual power, are among the most prominent symptoms. The diagnosis, when these symptoms are present, is based upon the finding of sugar in the urine. The percentage varies from 3 to 5 per cent. or over. In the acute cases the course is rapid and the disease is almost inevitably fatal. In the chronic cases the condition is not so serious and the patients may live for many years. Among the complications the commonest is pulmonary tuberculosis, the most serious diabetic coma. The presence of β—oxybutyric acid or diacetic acid in the urine is relied upon as a sign of approaching coma. The commonest form is the *dyspnœic*. The condition may be introduced by lassitude, headache, etc., followed by restlessness. Speech becomes incoherent, and the patient lapses into coma.

Although physicians have been warned repeatedly against confusing glycosuria with diabetes, a clear distinction between the two is by no means generally made. The " polyglandular " theories of the Viennese school take no account of the distinction between, for example, adrenin intoxication and true diabetes.

The work of Mehring and Minkowski referred to above led to a great deal of investigation and to much controversy. Many authors stated that diabetes did not always occur when the pancreas was removed. But this was supposed by the supporters of Minkowski to be due to incomplete removal. Pancreatic feeding seemed useless in diabetes and it was not always possible to find any lesion of the pancreas in cases of diabetes. Considerable stress was laid, moreover, upon the differences between diabetes in the human subject and the condition induced in animals by extirpation of the pancreas. But more recently it has been found that diabetes may be induced artificially in a dog if a sufficient portion of the pancreas be removed, leaving the remainder with its normal blood supply and its normal connection with the duct. In such cases the progress of the disease is hastened by carbohydrate feeding. Changes in the islets have been described in such cases.

The chief differences which are alleged to exist between clinical and experimental diabetes are as follows. The dextrose—nitrogen ratio is said to be 3·65 in severe human diabetes, while in the dog after extirpation of the pancreas it is not more than 2·8. The increase of total metabolism in the depan-

creatized dog is said to be greater and more frequent than in human subjects with diabetes. The changes found in the islets of Langerhans in human diabetes are not so striking as in dogs after removal of large portions of the pancreas. Finally, dogs with experimental diabetes rarely die of coma, while this is notoriously a common ending in the case of human beings with diabetes. Allen, who has carried out a great amount of painstaking work on this subject, points out that dogs have much less tendency to ketonuria than man, and believes that experiments upon animals of other species may give a result more nearly approaching human diabetes. He is inclined to believe that explanations may be found for the other differences enumerated.

Nothing is certainly known about the nature and origin of the acidosis and the diabetic intoxication which gives rise to coma. It is generally believed, however, that ketones are formed as a result of an incomplete destruction of fat, due to an imperfect consumption of carbohydrates. The ketones become oxidized to acetoacetic and β—oxybutyric acids. The condition is often referred to as *ketosis.* The intoxication seems largely due to the increased acidity, an increased H—ion concentration,

After extirpation of the pancreas in dogs and cats, Loewi produced dilatation of the pupil by the installation of adrenin. He attributes the dilatation to an increased excitability of the sympathetic nervous system. The reaction has been used as a test for pancreatic deficiency in the human subject, but does not appear to be very reliable.

Organotherapy—treatment with pancreas or extracts made from it—appears to be useless. The most modern form of treatment and, so far as can be judged from the clinical evidence available, the most successful form, is by fasting, combined with vigorous exercise. These measures, at any rate, prolong the life of the patient and render him useful and comfortable, even if they do not cure. As Allen points out, what is required is some means of strengthening the weakened function as well as giving it a rest. There can, however, be little hope for this till we are quite clear about the pathogenesis of the condition.

A functional relationship between the islets of Langerhans and the reproductive organs is claimed by some observers

and a similar relationship between the spleen and the pancreas has been suggested by certain authors.

An important function of the pancreas appears to be to increase the resistance of the body towards bacterial infection.

Extracts of pancreas are employed medicinally in gangrene and tuberculosis, as well as in pancreatic diabetes. The use of such extracts with the object of increasing the resistance to infection is of recent date, but is deserving of further practical study.

CHAPTER VII

THE INTERNAL SECRETION OF THE KIDNEY

A BELIEF in some kind of internal secretion on the part of the kidney has existed since the period when interest in the subject was stirred by the researches of Brown-Séquard. We have already seen (p. 25) that some writers have described pressor effects as the result of the injection into animals of extracts made from the kidney. Lewandowsky, however, found that with 5 to 6 centimetres of the blood from the renal vein no more positive result upon the blood-pressure was obtained than with a similar amount of blood taken from any other vein in the body. He concludes that no specific pressor substance is poured out from the kidney by the renal vein. The present writer has frequently tested the effects of different kinds of kidney extracts upon the blood-pressure. Sometimes there is a slight rise of pressure, sometimes there is no rise, or there may be a fall. The rise is never very marked, and only occurs with unboiled "protein" extracts. The same result may frequently be obtained from extracts made from other organs and tissues, and it may probably be concluded that, so far as the question of internal secretion is concerned, the results are not of any great importance. Further, it may be stated as probable that the high blood-pressure and hypertrophy of the heart in nephritis bear no relation to the presence of a pressor substance in kidney extracts.

But arguments based upon experimental work of a different character and upon clinical and therapeutical observations have been urged in favour of the view that the kidneys furnish an internal secretion. Brown-Séquard in 1869, had expressed the opinion that the phenomena of uræmia were not entirely due to the accumulation of urinary constituents in the blood, but to the absence of the normal internal secretion, or, as he expressed it, due to "l'existence de changements chimiques

morbides du sang remplaçant la sécrétion interne normale." This view was partly based upon clinical observations in which in spite of long-continued anuria the symptoms of uræmia were practically absent. Later, in 1892, Brown-Séquard and d'Arsonval stated that "le rein a une sécrétion interne d'une grande utilité." They removed both kidneys from rabbits and guinea-pigs, and found that death occurred much earlier than after ligature of both ureters, although, of course, in both cases there was an accumulation of urinary substances in the blood. Then they administered to some of these by subcutaneous injection diluted juice of kidney from a normal animal of the same species, while they left others untouched as controls. They found that those animals which had received the injection survived one or two days longer than the controls; the duration of life in the injected animals was, in fact, equal to or longer than that of animals which had undergone ligature of both ureters. The phenomena of uræmia were of slower development in those animals which survived the longer, owing to treatment with kidney extract.

Some observations of Lépine seemed to point to the fact that the kidney blood contains peculiar substances. Working with rabbits, this observer found that tying both ureters induced death after fall of temperature, vomiting, and diarrhœa. But if the flow through the ureter were checked by connecting it with a vessel containing normal saline at a higher pressure than that in the ureter, then the symptoms induced were quite different. Instead of a fall of temperature there was a rise, and in addition one observed increased rate of respiration and convulsions. A watery extract of kidney injected into the circulation produces, according to Lépine, a rise of temperature and dyspnœa. He concludes that the kidney substance contains materials inducing these effects, and suggests the possibility of auto-intoxications of renal origin.

E. Meyer, a pupil of Brown-Séquard, found that while the blood of uræmic animals produces no definite effects upon normal animals, when injected into nephrectomized animals, it induces dyspnœa and slowing of respiration. The same observer further found that injections of kidney extract, or normal blood, or of renal venous blood from a normal animal, have the immediate effect of checking the Cheyne-Stokes respiration which is such a striking symptom of uræmia.

Vitzou found that in rabbits and dogs the injection subcutaneously and intravenously of defibrinated blood from the renal vein of a normal animal prolonged the life of a nephrectomized animal in a very striking manner. Thus in one rabbit the survival was forty-two and a half hours longer than was the case with the control, which had, like the first, undergone double nephrectomy. Vitzou concludes that the kidney has an important internal secretion, the absence of which plays an important part in the causation of uræmia.

Many experiments of a similar character have been performed. Some of these have been in favour of the views expressed by Meyer and Vitzou, some have been opposed to them. The results obtained have been in fact very contradictory. Thus Chatin and Guinard investigated the question as to whether, by injection of blood from the renal vein of normal dogs into nephrectomized animals, there was any lengthening of life, or a diminution of the uræmic symptoms. The results were completely negative—that is to say, the animals treated with the serum died on the whole sooner than those not treated. Chatin and Guinard do not, however, definitely deny an internal secretion on the part of the kidney, for which they think there is a certain amount of clinical evidence.

It is doubtful if much importance can be attached to the results obtained by Vitzou. His work has been severely criticized by Lewandowsky, who points out that as a matter of fact animals can live from three to five days after double nephrectomy; whereas Vitzou states that he succeeded by his treatment in causing them to live sixty to sixty-nine hours instead of thirty-four! As pointed out by Biedl, the duration of life of nephrectomized animals is extremely variable. According to his own experience in some cases dogs and rabbits may survive as long as five or six days after extirpation of both kidneys, while in other cases they may die in thirty-six hours. Again, the incidence and course of the symptoms of uræmia in such animals is no criterion of their actual condition. It frequently happens that nephrectomized animals show no characteristic symptoms for two, three, or even four days, and then suddenly succumb. Others, on the other hand, on the day after the operation, suffer from vomiting and dyspnœa, then either recover or remain in a chronic condition of uræmia for several days. Such experiments are of little value as

demonstrating an internal secretion on the part of the kidney, and still less as pointing to the treatment of nephritis in man by means of kidney extracts. Notwithstanding this certain writers report good results in cases of chronic nephritis after treatment with kidney extracts by the mouth.

Lindemann found that guinea-pigs, after having received injections of rabbit-kidney emulsions, furnished a serum which was very toxic to rabbits, giving rise to albuminuria and uræmia. The injection of this nephrolytic serum provokes symptoms precisely similar to those induced by true kidney poisons. Here we have the formation of certain specific substances formed in the blood under the influences of the processes of absorption of the renal substance injected, and these are the substances which affect the kidney. Schültze could not observe the nephrotoxic effect of the serum of rabbits into which he had injected an emulsion of guinea-pig kidney. This observer also could not confirm the hepatolytic effect of the sera of animals which had been injected with liver emulsion, although Delezenne and Deutsch affirm that animals into which one injects liver emulsions furnish a serum which possesses powerful hepatotoxic properties.

Néfédieff believes firmly in a specific nephrotoxic serum in Lindemann's sense. He states further that this serum is also hæmolytic. The serum is analogous to the cytotoxins in general. Under the influence of hypodermic injections of kidney emulsion from healthy animals there appear in the blood of rabbits and guinea-pigs certain substances which exercise an injurious effect on the kidneys of the species of animal whose organs have been used in the preparation of the emulsion. Néfédieff found also that the serum of rabbits in which one of the ureters had been tied soon acquires powerful nephrotoxic properties. He suggests that in this case substances pass from the kidneys into the blood just as they do when an emulsion of the kidney has been injected.

Arguments of an analogous kind have also been used to explain the causation of œdema in nephritis. Kast observed that the blood of nephritics with œdema contains a lymphagogue substance of great strength, which also passes out into the dropsical fluid. Blanck noted, in investigating the serum of animals with uranium nephritis and uranium œdema, and of rabbits with chromium or aloin nephritis (which does not give

rise to œdema), that if one injects rabbits with serum or œdematous fluid from a rabbit affected with uranium nephritis, one gets œdema in this case also. Timofeen, from a review of the work of previous experimenters and on the basis of his own investigations, believes that the cause of the œdema in nephritis is the passing into the blood of certain lymphagogue substances, the source of which is a substance he calls "nephroblaptin" arising in the diseased kidney.

A discussion of this question would not be complete without a reference to the work which has been carried out upon the influence of the kidney on metabolism. Sir J. Rose Bradford removed portions of the kidney from animals, and subsequently studied their metabolism. He obtained results which suggested that when the amount of available kidney substance is greatly reduced the tissues of the body, and more especially the muscles, rapidly break down and liberate urea. But he states that he has no observations to show whether this is dependent upon the cessation of the action of an internal secretion supplied normally by the kidney.

Biedl performed a series of experiments of a similar nature upon dogs. He excised wedge-shaped pieces of the kidney, removing about a quarter of a kidney, and sometimes removed the whole of the other kidney in addition. It was found that after such operations the quantity of urine secreted was notably increased, even up to two, three, four, or five times the original amount. At the same time the total nitrogen excreted was much increased. V. Haberer also reports polyuria after excision of portions of the kidney substance. It is not possible to state whether these changes are really due to a deficiency in a normal process of internal secretion on the part of the kidney.

Notwithstanding the conflicting nature of the evidence as to an internally secreting function of the kidney, many authors insist that renal hormone therapy is of considerable value in many cases. Many French writers recommend kidney extracts in nephritis, but it is usually advised to persist in ordinary measures of treatment and to employ the renal extracts as adjunct remedies.

CHAPTER VIII

THE INTERNAL SECRETION OF THE INTESTINAL MUCOUS MEMBRANE AND THE NORMAL MECHANISM OF THE SECRETION OF THE PANCREATIC JUICE

It was first observed by Claude Bernard that the secretion of the pancreatic juice is dependent on the passage of food into the duodenum, and it has long been known that in the dog the flow of pancreatic juice, although it begins immediately after food has been taken, does not reach its maximum till either the first or the second hour, but more commonly is not reached until the third or fourth hour. It is to be noted that this is at a time when the greatest quantity of food from the stomach contents is passing into the duodenum. There has been much laborious investigation and a continued keen controversy as to the causal relationship existing between the passage of food through the pylorus and the secretion of pancreatic juice.

It will be interesting to glance at the state of knowledge on this subject in the year 1889. This can be conveniently done by recalling the exposition in a standard textbook of the period. M. Foster says: "Stimulation of the medulla oblongata or of the spinal cord will call forth secretion in a quiescent gland, or increase a secretion already going on. From this we may infer the existence of a reflex mechanism, though we cannot as yet trace out satisfactorily the exact path of either the afferent or the efferent impulses; all we can say is that the latter do not reach the pancreas by the vagus, since stimulation of the medulla is effective after the section of both vagi.

"A secretion already going on may be arrested by stimulation of the central end of the vagus, and the stoppage of the secretion which has been observed as occurring during and after vomiting is probably brought about in this way. This

effect, which, however, is not confined to the vagus, stimulation of other afferent nerves, such as the sciatic, producing the same effect, may be regarded (in the absence of any proof that the result is due to reflex constriction of the pancreatic and local vessels unduly checking the blood-supply) as an inhibition of a reflex mechanism at its centre in the medulla or in some other part of the central nervous system, much in the same way as fear inhibits at the central nervous system the secretion of saliva following food in the mouth. But if so, then we must regard the secretion of pancreatic juice as closely resembling that of saliva, inasmuch as it is called forth by a reflex act. Yet it is stated that, unlike the case of saliva, the secretion of pancreatic juice continues after all the nerves going to the gland have been divided, an operation which would do away with the possibility of reflex action. Such an experiment, however, cannot be regarded as decisive, since it is almost impossible to be sure of dividing all the nerves."

It is interesting to note how the one single observation (secretion after severance of all nerves), which at this period had to be opposed to the theory of reflex stimulation, was dealt with by Michael Foster. At this date, then, and for some time later the prevailing view was that the flow occurring when the acid chyme passed into the duodenum is due to the action of a reflex arc; but the observations of Bernard, Heidenhain and Pavlov, incorporated in the above account by Foster, were inconclusive, and the results obtained in different experiments were by no means constant. In more recent years Pavlov and his pupils have multiplied ingenious experiments and developed a wonderful technique, have struggled hard to reconcile the conflicting statements of different observers, and with infinite ingenuity have sought to establish on a firm basis the theory of nervous action. In searching for the channels of the reflex, Pavlov showed that, if certain precautions be taken, one can bring about a flow of pancreatic juice by stimulating the vagus or splanchnics.

A great step in advance was made by Popielski and by Wertheimer and Le Page. These observers proved conclusively that introduction of acid into the duodenum still excites pancreatic secretion after section of both vagi and both splanchnic nerves or destruction of the spinal cord, or even after complete extirpation of the solar plexus. Thus it was

clear that ordinary reflex action was out of the question. Popielski concluded, therefore, that the secretion is due to a local, a peripheral, reflex action, the centres for which are situated in the scattered ganglia found throughout the pancreas.

Wertheimer and Le Page, however, made a very interesting discovery—namely, that secretion of the pancreatic juice could also be induced by the injection of acid into the lower portions of the small intestine, the effect, however, gradually diminishing as the injection was made nearer and nearer the lower end of the small intestine, so that no effect at all was produced from the lower two feet of the ileum. Secretion could be excited from a loop of jejunum entirely isolated from the duodenum. They concluded that, in this latter case, the reflex centres are situated in the ganglia of the solar plexus, but they did not perform the obvious control experiment of injecting acid into an isolated loop of jejunum after extirpation of these ganglia.

About this time Bayliss and Starling were engaged upon investigations into the local nervous reflexes concerned with movements of the intestine. These observers made numerous experiments to test the validity of a hypothesis such as that of Wertheimer and Le Page, but soon found that in the case of the pancreatic secretion they were dealing with an entirely different order of phenomena, and that the secretion of the pancreas is normally called into play, not by nervous channels at all, but by a chemical substance which is formed in the mucous membrane of the upper parts of the small intestine under the influence of acid, and is carried thence by the blood-stream to the gland cells of the pancreas.

The experiments of Bayliss and Starling confirmed those of previous observers in so far as they found that, after exclusion of all nerve centres except those in the pancreas, a secretion of pancreatic juice is obtained by the introduction of acid into the duodenum. But, as pointed out above, the *experimentum crucis* of taking an isolated loop of intestine, dividing the mesenteric nerves supplying it, and then injecting acid into it, had not been performed.

Bayliss and Starling found that when this was carried out a well-marked flow of pancreatic juice was brought about. They next cut out the loop of jejunum, scraped off the mucous

membrane, rubbed it up with sand and 0·4 per cent. HCl in a mortar, filtered and injected into a vein. The first effect was a considerable fall of blood-pressure, and, after a latent period of about twenty seconds, a flow of pancreatic juice at more than twice the rate produced at the beginning of the experiment by introduction of acid into the duodenum.

Bayliss and Starling suggest the name "secretin" for the active substance present in the intestinal extract, and the term has been adopted by subsequent workers. Secretin is probably produced by a process of hydrolysis from a precursor "prosecretin" present in the intestinal cells. It is not a ferment, nor is it of the nature of an alkaloid or diamino-acid.

The results obtained by Bayliss and Starling were confirmed by Camus and Gley and others, and Wertheimer demonstrated the presence of secretin in the blood flowing from a loop of intestine into which acid has been introduced.

In a later communication Bayliss and Starling announced that secretin can be prepared from the upper part of the intestine of any animal belonging to the class of vertebrata by scraping off the mucous membrane, pounding it up, and boiling with dilute hydrochloric acid.

The experimental evidence which is clearly put before us by Bayliss and Starling justifies the view that the normal sequence of events in the secretion of juice by the pancreas is as follows: The acid of the gastric juice upon reaching the duodenum converts the prosecretin manufactured by the epithelial cells into secretin; this secretin is then absorbed into the blood-stream, carried to the cells of the pancreas, and stimulates the organ to secretory activity. *The external secretion of the pancreas is the result of the internal secretion of the duodenal mucous membrane.*

The formation of prosecretin in the duodenum does not appear to take place as a response to the stimulus of ingestion of food. Pringle has quite recently found that secretin prepared from newly-born kittens, before suckling, gives a fairly active flow of juice when tested on a dog. When fœtuses of different periods were examined, it was found that some showed the presence of an active secretin, some did not.

In this most important discovery of Bayliss and Starling is

involved an important modification of our conception as to the empire of the nervous system. The production of secretin is, in fact, the best authenticated example of internal secretion which can be quoted. The hitherto most oft-cited examples, such as those of the adrenal body and the thyroid gland, are, in the opinion of the present writer, more distinctly hypothetical.

Beyond all doubt secretin is a powerful excitant of the pancreatic secretion, but its specific nature is denied by some authors. Bayliss and Starling admit that secretin acts to a small degree on the secretion of bile, and other authors state that it acts on the secretion of saliva and the gastric and intestinal juices. Again, while Bayliss and Starling affirm that secretin can only be obtained from the upper part of the small intestine, others assert that they have found this substance, though only in small amount, in other parts of the intestinal tract, and even in lymphatic glands.

Although Bayliss and Starling showed that the depressor substance in extracts of the intestinal mucous membrane is independent of secretin, and that a secretin solution can be obtained free from the depressor substance, yet this has not hindered Popielski and others from urging that the flow of pancreatic juice after injection of intestinal extracts is due to the lowering of the blood-pressure and consequent anæmic stimulation of nerve centres.

Fleig shows that secretin does not produce its effects by acting on the nerve endings in the intestinal epithelium, and the last-named author, as well as Wertheimer and Le Page, state that they obtained a secretion of pancreatic juice by injecting acid into an isolated loop of jejunum whose nerve communications were intact, and even when the venous blood of this loop is diverted, and the thoracic duct is tied off. Fleig concludes that the mechanism of secretion of pancreatic juice after the injection of acid into the upper part of the small intestine is, under normal conditions, of a double character: (1) Secretin calls forth secretion of pancreatic juice by direct action on the cells of the pancreas. (2) Acids, independently of the formation of secretin, cause a secretion of pancreatic juice by reflex nervous action.

These two secretions are said by Sawitsch to present quite different characters. The latter is thick, opalescent, rich in

enzymes and proteins but poor in alkalies. The chemical secretion, on the contrary, is thin and watery, contains little enzyme or protein, and is rich in alkali.

Gley has recently given the accompanying classification of substances which excite the flow of pancreatic juice (p. 63).

Gley points out that the part played by the acid of the gastric juice as an excitant of the flow of pancreatic juice is altogether special, since it acts at the same time through the chemical mechanism in liberating secretin, and by means of a nervous mechanism, that is to say, by reflex excitation of the secretory nerves to the pancreas.

V. Fürth and Schwarz believe that secretin is not a definite, single substance, but a mixture of several gland-stimulating substances, of which choline can be recognized as one.

With regard to the mechanism of the secretion of the intestinal juice, nothing definite is yet known. We know that the juice when it is formed is essential for the activation of the pancreatic juice by means of the enterokinase. The trypsinogen is only converted into the proteolytic ferment trypsin after the action of the enterokinase. According to Pavlov, the secretion of the succus entericus depends upon two factors: (1) The mechanical distension of the alimentary canal; (2) the presence of the pancreatic juice. Bayliss and Starling consider it probable that the secretion of succus entericus is called forth by the chemical action of the pancreatic juice upon the glands in the intestinal wall. Delezenne and Frouin report that the intravenous injection of secretin provokes an immediate and abundant secretion of succus entericus.

It has been suggested that the increase in red and white cells in the blood after a meal is due to the stimulation of the bone-marrow by secretin.

According to Lombroso the prime factor in the secretion of the intestinal juice is the action of chemical substances which are produced during normal digestion, and act on the nerve endings of the mucous membrane of the intestine.

It has been suggested that secretin may be useful as a drug with the object of increasing the pancreatic flow. But it must be noted that it is absent from some commercial preparations supposed to contain it, and even if it is present it would be destroyed quickly by the gastric juice and the trypsin. It

SYNOPTIC TABLE OF EXCITANTS OF THE PANCREATIC JUICE

Indirect Excito-secretory Substances. By Formation of Secretin.			Direct Excito-secretory Substances. By Penetration into the Blood.	
Solvents *in vivo*.				
Exogenous.	Endogenous.	Solvents *in vitro*.	Natural Excitants (Absorbable Products of Functional Activity).	Artificial Excitants.
Acid beverages Neutral fats Mustard } Alimentary	The acids of the gastric juice (HCl especially) Soaps	Acids Fats and soaps Concentrated solutions of neutral salts Solutions of NaCl at 100° C. Warm water [2]	Albumoses	Pilocarpine Physostigmine Muscarine Trimethylamine
Acids [1]	Albumoses		Choline	
Chloroform . . . . Chloral	Alcohol Chloral Essence of mustard			Chloral Ether

[1] With this reservation, that the matter is not fully proved *in vivo*.
[2] The action of warm distilled water is not constant.

might perhaps be administered subcutaneously, but the results of such administration have been negative in cases where it has been tested.

At the present time there is little or no sound physiological basis, as there is no certain clinical evidence, for the value of secretin in treatment of disease.

CHAPTER IX

THE INTERNAL SECRETION OF THE GASTRIC MUCOUS MEMBRANE AND THE NORMAL MECHANISM OF THE SECRETION OF THE GASTRIC JUICE

It has been shown by Pavlov that psychical secretion, as well as the results of a sham meal, are entirely abolished by division of both vagi, and, further, that stimulation of the peripheral end of the cut vagus (after its cardio-inhibitory fibres have been allowed to degenerate) calls forth a steady secretion of gastric juice. These experiments show conclusively that an important —probably the most important—part of the gastric secretion is determined by a nervous mechanism.

On the other hand, Ducceschi finds that dogs and cats whose stomachs have been severed from any nervous connections either with the central nervous system or with the semilunar ganglion, show no particular disturbances.

However important the nervous influences may be, it is possible that the nervous secretion does not account for the whole of the gastric juice obtained as the result of a meal.

The question as to the existence of some specific hormone in relation to gastric secretion analogous to secretin was put to the test by Edkins. This observer found that extracts made of the pyloric mucous membrane in boiling water or HCl 0·4 per cent. contain an active substance, which, on injection into the bloodvessels of an animal, leads to a secretion of gastric juice. Extracts made in cold water, peptone, glucose, or glycerin also contain variable amounts of this substance.

Extracts of the fundus mucous membrane, however made, do not contain this substance. The inactive condition of some extracts is due to the substance being present in an undeveloped state ; boiling the substance or treating with acid will lead to the complete development. This is, however, only the case with extracts made from the pyloric or true cardiac mucous

membrane, but not the fundus mucous membrane. Atropine does not diminish the reaction of an animal to this excitant. The substance is not a ferment, as boiling an extract leads to an increase rather than a diminution of its properties.

From these experiments it would seem that we are justified in concluding that the first products of digestion act on the pyloric mucous membrane, and produce in this membrane a substance which is absorbed into the blood-stream and carried to all the glands of the stomach, where it acts as a specific excitant of their secretory activity. This substance may be called the *gastric secretin*, or *gastric hormone*. It exists in the mucous membrane in the form of a precursor (*progastrine*) which is activated by the boiling water or the hydrochloric acid.

In the normal secretion of gastric juice there is a nervous secretion due to the secretory fibres in the vagus, and a chemical secretion due to the chemical stimulation of the secretogogues or of the hormones produced by them.

The investigations carried out in Pavlov's laboratory seem to indicate that the quantity as well as the properties of the secretion vary with the character of the food.

Many physicians believe that preparations of the gastric mucous membrane have a therapeutic influence, probably due to their hormone content. Some of these extracts are employed in place of pepsin.

CHAPTER X

THE INTERNAL SECRETION OF THE REPRODUCTIVE ORGANS

A. The Internal Secretion of the Testis

Some of the effects due to the absence of the internal secretion of the testis have been known from the remotest times. The transformation of the bull into the ox and the cock into the capon are examples which will occur at once to the reader.

Brown-Séquard found that subcutaneous injections of extracts of testis exercised considerable influence upon the general health, as well as the muscular power and mental activity. The experiments were performed upon himself when he was seventy-two years of age, and he describes very marked rejuvenating effects. It is probable that some at least of Brown-Séquard's personal benefit under this treatment is to be attributed to suggestion.

More recently Poehl asserts that he has prepared a substance, *spermin*, to which he assigns the formula $C_5H_{14}N_2$, which has a very beneficial effect upon the metabolism of the body. He believes that this spermin is the substance which gives to the testicular extracts prepared by Brown-Séquard their stimulating effect. He claims for this substance an extraordinary action as a physiological tonic. It is recommended that testicular preparations be employed in cases of deficiency of testicular substance, or in old age, when the testes lose their functional capacity. Zoth and Pregel seem to have obtained definite proof, by means of ergographic records, of the stimulating action of the testicular extracts upon the muscle-nerve apparatus in man. They find that injection of such extracts not only causes an increase in the amount of muscular work which can be accomplished, but lessens the subjective fatigue sensations.

The chemical composition and physiological action of Poehl's spermin and other orchitic extracts have also been investigated

by Dixon. He finds that the preparations contain a very large amount of nucleo-protein and other proteins, some organic substances unaltered by boiling, and inorganic salts. Injection into the circulation caused a fall of blood-pressure, but this we now know is an action common to all tissue extracts. Walker is doubtful of the efficacy of testicular medication, stating that the injection of fluid extract into castrated dogs had no effect in arresting the atrophy of the prostate gland.

It is exceedingly doubtful how far the effects of subcutaneous injection of orchitic extracts are to be regarded as specific. Fresh (unboiled) extracts of various organs and tissues of the body have a distinct stimulating effect when administered subcutaneously to dogs, cats, and other laboratory animals.

There are, however, reasons of quite another kind for thinking that the testis pours into the blood-stream certain materials which are essential for the proper development of the body and the maintenance of normal health and vigour. The condition of persons or animals in whom the testes have not descended, or from whom the testes have been removed, is strong evidence that, besides the function of the preparation of the specific reproductive elements, the organs have other important duties to perform. There seems to be no doubt that the secondary sexual characters in the male are due to an internal secretion on the part of the testis. Castration before the age of puberty in man is well known to prevent the growth of hair on the face, to arrest the growth of the thorax, and pelvis, and the larynx (and so preserve the voice of childhood). It is stated that the practice of castrating boys for the cathedral choirs in Rome was carried out until 1878. Male sopranos or "sopranists" were formerly a leading feature of musical life. "A peculiarly soft and full quality of tone seems to have been the characteristic of these *evirati*, who, as a class, disappeared from the operatic stage with Velluti, who retired about 1829, and died as late as 1861."[1] The effect on the larynx is noticed also in horses and cattle when the testes are extirpated in early life. There is in many eunuchs a tendency to a certain form of gigantism, and the mental characteristics are peculiar.

The first result of castration before the age of puberty is the hindrance to further development of the reproductive appara-

[1] *Oxford History of Music*, Vol. IV., F. Maitland, 1902.

tus. The vesiculæ seminales and the prostate are small and atrophied. The penis does not share in the atrophy, so that in Eastern countries it is frequently considered necessary to remove this as well as the testes. The atrophy of the vesiculæ seminales and the prostate after castration can also be noted experimentally in animals; and, further, if castration be performed in quite young animals, the operation prevents the development of the prostate, whereas division of the vas and the abolition of the production of semen have no arresting influence. The atrophy of the prostate after castration led to the introduction of this operation as a method of treating prostatic enlargement. Castration on one side produces no effect, the retention of a single testis being sufficient to maintain the functional integrity of the prostate. It is stated, also, that Cowper's glands atrophy after castration. It is generally assumed that the growth and integrity of the prostate are determined by a hormone furnished by the testis. On this hypothesis we might explain hypertrophy of the prostate as due to a hypersecretion of the hormone. This would not be inconceivable if we make the further hypothesis that the internal secretion proceeds from the interstitial cells of the testis, and these might still be active, or even of increased activity at a time when the seminiferous tubules are in process of degeneration.

So much for the influence exerted by the testis, in all probability by means of an internal secretion, upon the growth and development of the other generative organs. We have now to consider the influence of the testis in developing and maintaining the secondary sexual characters. It is, perhaps, well to point out that castration never induces a condition in any respects resembling the female type; the condition is infantile, and not female. The effects in man are well known, and have already been briefly referred to. The relation between testis and secondary sexual characters is, however, closer in those animals in which we find increased testicular activity in the breeding season associated with a periodic development of other sexual characters. An example is given by Marshall. In the male elephant the glands on the side of the face emit a musky secretion during rut.

If the testes are extirpated from quite young stags, the antlers never develop; if the operation is performed at the

period when the antlers have just begun to grow, these remain covered by skin, forming the "peruke" antlers. If castration be carried out after complete development of the antlers, these are shed prematurely, and replaced by imperfect structures. Analogous results are recorded in the fallow deer and prong-buck (*Antilocapra americana*). As pointed out by Marshall, it is of interest to note that in the eland and in horned cattle, where both sexes possess horns, the growth and development of these structures are not affected by castration.

Changes in the bodily conformation as a result of castration in quite young animals also occur in sheep, guinea-pigs, oxen, and other animals. In the case of the cock, it is well known that castration arrests the development of the comb and spurs.

Experiments of a somewhat different nature must now be referred to. Bouin and Ancel tied the vasa deferentia in different animals. The result of this operation was that the seminiferous tubules atrophied, while the interstitial cells were unaffected. These authors were the first to point out the distinctly glandular appearance of these interstitial cells. They suggest that it is owing to the presence of the interstitial tissue that the secondary sexual characters become developed, and that this is due to the activity of a definite internal secretion on the part of the interstitial cells. Bouin and Ancel report further that subcutaneous injection of extract of the interstitial tissue in guinea-pigs diminishes the effects of castration, and tends to promote growth. In a still further communication, these authors state that the development of the interstitial glandular-looking tissue coincides with the first occurrence of spermatogenesis. Other authors also lay great stress upon the importance of the interstitial cells of the testis.

Shattock and Seligmann have also studied the effect of the occlusion of the vasa deferentia in sheep and fowl, and find that this does not hinder the full development of the secondary male characters. Since castration does hinder this development, it follows that the metabolic results arising from the functions of the testis must be attributed to the elaboration of an internal secretion and its absorption into the general circulation. These authors agree with Bouin and Ancel that the interstitial cells of the stroma have characters so unmistakably glandular that some secreting function must be

assigned to them, and they may possibly be responsible for the internal secretion just referred to.

There is an important difference in the result obtained when the whole cord is ligatured from that obtained when the vas only is tied. In the former case all sexual activity comes to an end; in the latter, after a short interval of time, the animal remains just in the same condition as the control, although, of course, reproduction is impossible in both cases. After ligature of the vas the interstitial cells remain unaltered, although the spermatogenic tissue degenerates. These results, pointing distinctly to an internal secretion on the part of the interstitial cells of the testis, have been furnished to me by Dr. Copeman. His results are generally in agreement with those of Bouin and Ancel.

Foges in 1899 could not be sure that transplantation of the testis had any influence on the secondary sexual characters. In a later paper he states a different conclusion. The experiment he performed was to remove the testes of fowls and transplant them to abnormal positions in the body cavity. In these later experiments—at any rate, in those which were successful, the transplanted testes had a similar influence upon the development of the secondary sexual characters to that of the normally placed testes, and the comb and spurs were developed just as in uncastrated cocks. From these experiments Foges draws the conclusion that the testes are organs furnishing an internal secretion which controls the development of the male characters.

Shattock and Seligmann have also performed some experiments upon testicular transplantation in fowls. They report that the secondary sexual characters develop to a varying extent, which seem to depend on the amount of testicular substance left behind.

It has been alleged that the development of male characters followed the injection of extracts of testis. The injections were made into hens, and the combs and wattles grew in size, and became more brightly coloured. These experiments require confirmation.

Very important indeed, as bearing on the question of the internal secretion of the testes, are the experiments of Nussbaum. At the approach of the breeding season there is formed in the male frog a thickened pad of skin on the first digit of each

fore-limb, associated with an increased muscular development in the forearm. This modification is preparatory to the act of copulation, when the male frog uses its arms in embracing the female, and so assists in pressing out the eggs from the oviduct. If the male frog be castrated, the pad is not formed, and the muscles do not develop. Nussbaum found that when pieces of testis were introduced into the dorsal lymph sac of a castrated frog, the swelling on the thumb and hypertrophy of the muscles of the leg took place just as though the frog had not been castrated. This development of a secondary sexual characteristic must have been due to the absorption of substances (internal secretions) derived from the testicular tissue, since there was no nervous connection. If, however, the nerves supplying the muscle of the forearm were severed (in an entire frog) the enlargement did not occur. A similar result was brought about on transsecting the nerve supplying the glands and papillæ of the thumb-swelling. Nussbaum concludes, therefore, that the internal secretion provided by the testis acts through the medium of the nerves. It has, however, been pointed out that in similar cases it has been shown that the apparent effect of the transsection of nerves is due to the loss of sensibility in the parts concerned, in consequence of which the tissues are not guarded from injury.

Transplantation of the testis was carried out by Hunter and by Berthold, and, apparently, with complete success. In cocks Berthold found that the secondary sexual characters were retained after transplantation, and the author puts forward what is practically the modern view of internal secretion, except that he considers the nervous system to play an important part.

A subject of peculiar interest is the influence of the testis upon growth in general, and upon the growth of bone in particular. There has long been a belief in a definite antagonism between growth and sexual activity. It was laid down as a general biological principle by Carpenter, Spencer, and others, that the functions of nutrition and reproduction are essentially opposed to one another, because reproduction makes such a demand upon the parent for material that the supply for nutrition and growth of the parent is lessened. This philosophical generalization has been vigorously combated by Minot, Morgan, and others. However this may be, abundant evidence

has now been accumulated that the absence of the functional testis brings about abnormal growth of bony tissues. But this, according to modern views, is not due to the fact that the testis is not acting as an organ of reproduction, but to the fact that the normal internal secretion from the organ is not available for the controlling of the growth of bone in the body.

Poncet in 1897 reported a series of experiments upon rabbits, in which he found that castration has a very definite effect upon the development of the skeleton. The bones of the castrated animals were stronger, but especially longer, than those of the controls. The increase in length was particularly noticeable in the femur, the tibia, and the fibula. The whole skeleton of the castrated rabbit was, however, somewhat larger than that of the control. The fact that the presence of a functional testis is inimical to bone growth is also emphasized by Lortet and by Pirsche. The work of Pirsche firmly established the fact that castration in youth is followed by abnormal growth of the long bones. Geddes has recently reinvestigated several points in connection with the matter. He reports that males whose testicles are functionless are found to possess unduly long limbs. This undue length affects the radius and tibia more than the humerus and the femur. The process of ossification is unduly prolonged. He finds, also, that in animals which have been castrated there is an increase in the length and weight of the bones, and a delay in the obliteration of the epiphysial cartilages. In eunuchs there is delay in the completion of the process of endochondral ossification. Further, the long bones of the appendicular skeleton are unduly long. This excess of length is particularly remarkable in the more distal segments of the limbs. The bones are thin, smooth, and slender. Geddes is inclined to look upon these results as occasioned by the setting free for general use of foodstuffs which would otherwise have been used to provide for the drain of spermatogenesis. In other words, the activity of the sexual glands is opposed to body-growth. Apparently there are no experiments to determine whether simple vasotomy or ligature of the cord itself will induce these bony changes. If simply abolishing the spermatogenesis will bring about these changes, it is obvious that the theory of internal secretion would have to be abandoned.

Loisel believes that one of the functions of the internal

secretion of the testis is to destroy fat in the body. For this reason men are thinner than women, and castrated men become fat.

The view that the internal secretion of the testis which is responsible for the secondary sexual characters is derived from the interstitial cells of Leydig is strongly supported by the facts that these cells have the characters of secretory cells (fatty granules and mitochondria), that the animal remains normal even when there is atrophy of the seminiferous tubules (after tying of vas deferens), and that it is only when we remove the atrophic testis with the Leydig's cells then in good condition, that we produce the changes that are noted after castration. (Massaglia.)

It is stated (Wheelon and Shipley) that castration causes a depression of the vaso-motor irritability and that transplantation partially reinstates normal activity.

In the human subject Lichtenstern reports that after loss of both testes, transplantation of a testis from another man restores the previous physical and psychical condition.

Brown-Séquard's work has already been referred to, and a summary of the alleged beneficial results from the use of Poehl's spermin has been given. Orchitic extracts have also been recommended in certain toxic dermatoses, and even in psoriasis, with the idea that they have an antitoxic action. In asthenia and nervous irritability it is stated that the extracts of testis are useful and far-reaching in their results.

B. The Internal Secretion of the Prostate Gland

It has been reported that after prostatectomy in dogs the testicles gradually lose their functional activity, ejaculation ceases to occur, the formation of spermatozoa is stopped, and the other generative secretions are no longer formed. On the other hand, the administration of glycerin extract of prostate to dogs so operated upon prevents the atrophic changes; ejaculation continues, the spermatozoa do not disappear, the preputial glands secrete. It is inferred, therefore, that the functional activity of the testis and other generative organs is dependent upon an internal prostatic secretion.

Walker had previously obtained contrary results with white mice. As Marshall very justly points out, the most obvious

criticism of the theory of prostatic internal secretions is that it is unlikely on phylogenetic grounds, that the functional activity of the essential organ of reproduction should depend on the presence of an accessory gland of comparatively recent evolutionary development. Further, Dr. Halpenny, working in my laboratory, has repeated the experiment upon dogs. In these there was certainly no appreciable effect upon the testes.

There are several reports of cases of prostatic enlargement in which good results are said to have followed the administration of extract of prostate. Such extracts are also affirmed to be of value in increasing the contractions of the bladder.

C. The Internal Secretion of the Ovary and the Corpus Luteum

The ovary in mammalia consists of a connective tissue stroma, with bloodvessels, lymphatics, and nerves, enclosing the Graafian follicles with the ova. At certain periods there are corpora lutea and atretic follicles, and in certain species the "interstitial gland."

Cyclical changes occur both in the ovary and in the uterus. In the ovary these consist of ripening of the follicle, ovulation, and formation of the corpus luteum. In the uterus we have to deal with the structural changes which accompany the œstrous cycle, consisting of growth of the mucous membrane with increased glandular activity, followed by regression and period of rest.

The quiescent period is called the "anœstrum." The "pro-œstrum" is distinguished by increased vascularization of the reproductive organs, which reaches a climax at the period of "œstrus" or "heat," during which only in the majority of animals the female will admit the male. In the human subject and the primates generally menstruation corresponds to pro-œstrum in the lower animals.

If conception occurs, œstrus is followed by gestation, lactation, and finally succeeded by another anœstrum. But if conception does not take place, œstrus is followed by metœstrum, during which there is a return to the normal on the part of the whole system.

The following scheme is given by Hill and O'Donoghue—

Ancœstrum

Pro-œstrum (uterine degeneration)

Œstrus (ovulation)

Pregnancy | Metœstrum
Nursing period |

Ancœstrum

In males, as we have seen, interference with the discharge of the seminal fluid has no effect on the secondary sexual characters, while removal of the testis has a very marked effect. Similarly in the female, any operation which abolishes the normal passage of the ova down the Fallopian tubes into the uterus has no influence on the secondary characters, while removal of the ovary results in the changes about to be described.

Our knowledge of the effects of extirpation of the ovaries before the age of puberty in the human subject is very limited. A fairly large number of operations must have been performed in which female children were deprived of both ovaries at an early age, but there seems to be no systematic account of them. Marshall states that such extirpation, if the operation be carried out before puberty, besides preventing the onset of puberty and the occurrence of menstruation, produces noticeable effects on the general form and appearances. He instances the case of certain adult women in semi-barbarous parts of Asia, where the natives perform this operation upon young girls. Such women are said to be devoid of many of the characteristics of their sex, and in certain cases to present resemblances to men. This account seems to be derived from the observations of Roberts in the East Indies. According to Biedl, however, there is no ovariotomy among such people, but simply a mutilation of the external organs of generation. Indeed, it seems incredible that savages could successfully perform double ovariotomy.

When extirpation of both ovaries is carried out in the human female after the age of puberty, the most marked effect is the cessation of menstruation. There is also in some cases an atrophy of the uterus, vagina, and external genitals. The effects on the breasts vary in different cases. Sometimes these

atrophy, while in other cases they appear to increase in size. This latter result, when it occurs, may be attributed to obesity, which is the usual result of the operation. It is difficult to obtain information as to the effects on sexual desire. It appears, however, that it may not be much affected for some time after the operation.

After extirpation of the ovaries it is stated that the hair becomes more luxuriant and the skin lighter in colour. The nipples become smaller and the pigmentation of the areolæ becomes less marked.

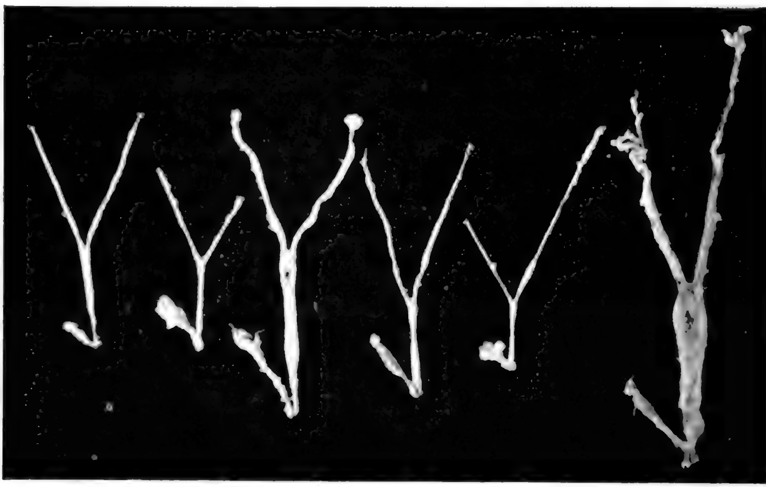
The metabolic results have not yet been fully worked out. In the human subject extirpation leads to a series of symptoms which are usually attributed to excitation of the autonomic nervous system. These consist of emotional disturbances, headache, fainting, intestinal disturbances, and feelings of heat and cold.

In some female animals removal of the ovary has been stated to lead to the appearance of male characters. Cases are recorded in which female deer possessed horns. In these the ovaries were abnormal or the animals were old. Similar cases are not uncommon in birds. Such cases are difficult to explain on any other hypothesis than that the secondary male characters are normally present in a latent form in the female, and that the ovaries exert an inhibitory influence over their development. As we have seen above (p. 69), castration in the male never induces a condition in any respects resembling the female type.

Carmichael and Marshall have furnished some further details of the effects of ovariotomy in rabbits. The degree of uterine degeneration was proportional to the time after the operation (see fig. 12.) After six months the organ was fibrosed and the glands had disappeared. The epithelium was greatly thinned and the muscle fibres disintegrated. The Fallopian tubes had undergone atrophy. When the operation was performed upon very young rabbits the uteri remained infantile. The same was the case with the Fallopian tubes. In dogs ovarian extirpation results in a marked increase in the vaso-motor response to a standard dose of nicotine. This phenomenon is interpreted as indicating overexcitability of the sympathetic nervous system (Hoskins and Wheelon). These effects are very similar to those observed after ovariotomy in the human subject.

All the foregoing facts show that the ovary, just like the testis, has a far-reaching influence on the metabolism of the body, this influence manifesting itself in helping to develop and maintain the secondary sexual characters. Until recently this influence has generally been supposed to be nervous. As we shall see below, the evidence as to one or several kinds of internal secretion is now tolerably conclusive.

Considerable attention has been paid to the subject of ovarian transplantation. Unfortunately there has been some confusion in the terminology. In the present section the term "autoplastic" will be used in cases where the organ is trans-



Group I II III IV V Normal

FIG. 12.—The effect of double ovariotomy on the growth of the uterus in young rabbits. The first five are the uteri from rabbits who had both ovaries removed on March 2, 1921, and were kept alive till June 7. Number 6 is a normal control. Note the effect of ovariotomy on the size of the uterus. No. 3 was a month older than the others. (Photo by Sutherland Simpson, from a class experiment carried out by students at Cornell University).

planted into some part of the body of the same individual. A "homoplastic" transplantation will refer to a graft made from one individual to another belonging to the same species, while "heteroplastic" will be the term applied to a graft from one animal to a second belonging to a different species.

In human beings ovarian transplantation has been carried out on many occasions, with varying degrees of success. Morris

reports a successful case of transplantation of the homoplastic variety. The ovaries from one woman were grafted into a second, and the latter gave birth to a child four years later.

Knauer was apparently the first to report successful autoplastic transplantation in animals. The ovaries were detached from their normal position and grafted upon the mesometrium or into the abdominal wall. A certain part of the grafted organ degenerated ; the rest of it gave rise to ova which were capable of fertilization. Atrophy of the uterus, an invariable result of castration, was prevented if successful transplantation of an ovary had been effected. Several other authors have obtained similar results. Some writers have reported that the offspring resulting from fertilization of ova from grafted ovaries indicate a "foster-mother" influence. Thus ovaries have been transplanted from hen to hen. Such fowls laid eggs which were duly hatched, and the chicks partook of certain of the foster-mother's characters.

Transplanted ovaries remain normal for a time, except that the germinal epithelium becomes absorbed. Sometimes degeneration occurs and the stroma may remain normal while the follicles disappear or are replaced by corpora lutea. Transplanted ovaries show the same cyclical changes as normal organs, *i.e.*, ovulation occurs in them. Autoplastic transplantation is more easily carried out than homoplastic, and the most successful cases are those in which two animals from the same litter are employed.

But ovarian grafts and their effects on the uterus are not permanent. Sooner or later degeneration takes place in the grafted organ and atrophy of the uterus takes place. According to A. Louise M'Ilroy, the rate of degeneration varies with the site of implantation, the more vascular the site, the longer the persistence of the graft. The corpora lutea first undergo a hyaline change and infiltration of leucocytes. Cystic degeneration overtakes the follicles, though the interstitial cells may persist for some time longer. Professor M'Ilroy considers that it is the interstitial cells which control the nutrition of the uterus, since atrophy occurs only when they are degenerated. The experiments so far carried out indicate that a grafted ovary may remain functional for a year or more.

Experiments carried out by Steinach show that if ovaries are grafted into young male guinea-pigs, the mammary gland

may develop and secrete milk. It seems likely that the interstitial cells are responsible for this effect.

Lipschütz concludes that the secretion of the gonads acts in a "sex specific" manner, that is, the male gland aids the development of male sexual characters only while it inhibits the female characters, whereas the female gland promotes the growth of female sexual characteristics, at the same time inhibiting male characters. In birds the development of the male plumage and the spurs does not depend on the male sexual gland, while the ovary converts a male plumage into a female one and inhibits the growth of spurs. The male plumage and the spurs are evolved out of the characters of the hypothetical non-sexual embryonic form, without any influence of the sexual glands. (See however p. 68.) The plumage and spurs become male sexual characters, not because of any action of the male gland on the non-sexual soma, but because the development of these non-sexual characters is influenced in the female by the internal secretion of the ovary. Accordingly Lipschütz classifies the sex characters as follows :—

1. Those non-dependent on the "puberty gland" (Steinach) or "interstitial gland."

2. Those dependent on the puberty gland, which calls forth the characters by acting on the non-sexual embryonic form in the direction of augmentation or inhibition.

Sand asserts that, by simultaneous transplantation of both ovary and testis into a castrated animal, he has succeeded in obtaining a true experimental hermaphroditism (somatic and psychic).

The results of ovarian transplantation in the human subject with the object of reducing the symptoms of the artificial menopause after ovariotomy seem to be encouraging. But if the uterus has also been removed, the retention of ovarian tissue is of little benefit.

Extracts of ovary do not contain any substance of special chemical or physiological interest. The pharmacodynamical effects of ovarian extracts are found to be the same as those of extracts from organs and tissues generally, viz., a temporary depression of the arterial blood-pressure brought about by dilatation of arterioles throughout the body. The substance or substances which produce this effect are not known. They are soluble in alcohol and in ether, as well as water. It has

been stated that there is a considerable difference in the activities of extracts from different animals. It is said that extracts of ovary raise the metabolism in castrated animals, and have a stimulating action on uterine contraction. It is doubtful whether these effects are specific.

A considerable amount of work has been carried out upon the structure and functions of the corpus luteum. This body in its fully formed state consists of columns of large cells (luteal cells) containing a yellowish pigment. The columns are separated by intervening trabeculæ, composed of fibrous tissue containing numerous bloodvessels. These trabeculæ converge inwards from the surrounding ovarian stroma to a central strand or plug of connective tissue, in which there are no luteal cells, occupying the axis of the nodule (see Fig. 13). The columns of cells are not unlike those of the cortex of the adrenal (see Figs. 13 and 13a). The fully developed corpus luteum is a highly vascular structure.

The fullest and most complete account both of the development and of the histology of the fully formed corpus luteum is given by Sobotta. In the mouse the epithelial cells are large and polygonal in shape, measuring 20 μ or more in diameter. The cells contain fat, which is mostly disposed excentrically, but it may almost fill the entire cell. The peripheral cells are for the most part free from fat, while those in the centre contain the largest amount. Generally speaking, the older a corpus luteum is the more fat does it contain. The nucleus is rounded. The connective tissue is in the form of spindle-shaped anastomosing cells. They surround groups of four to five epithelial cells by anastomoses of their processes. Their nuclei closely resemble those of the capillary walls. The connective tissue of the central plug consists of stellate elements. In some animals the fully formed luteal cells are rounded or spindle-shaped, and may show signs of degeneration.

The mode of formation of the corpus luteum is still under discussion. Former investigators were not able to agree as to whether the body is a connective-tissue structure, or whether the luteal cells are formed by the hypertrophy of the epithelial cells of the undischarged Graafian follicle. The former theory is that of v. Baer, the latter that of Bischoff. The investigations of Sobotta upon the mouse and the guinea-pig confirm Bischoff's view, but there have been several investigators

who could not adopt this theory. There is no need to enumerate the authors who have held one or the other view on this question. There is a tendency towards a compromise in some of the recent papers. Thus, van der Stricht found that, whereas the majority of the luteal cells are derived from the follicular epithelium, a certain number are developed out of interstitial

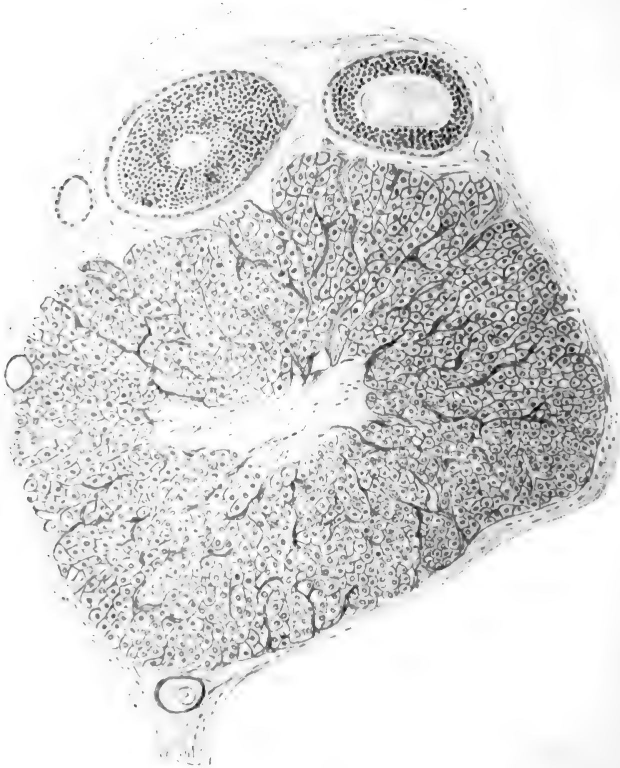


FIG. 13.—Section through the ovary of *Dasyurus viverrinus*, showing Graafian follicles and corpus luteum. (Drawn by Mrs. F. D. Thompson from material supplied by Prof. Charles O'Donoghue.)

cells in the inner theca of the connective-tissue sheath. As pointed out by Marshall, this is of special interest in view of the statement made by Miss Lane-Claypon that the follicle and interstitial cells have an identical origin, since both are derived from the germinal epithelium, and pass through a similar series of changes. The majority of recent investigators

are, however, in favour of the view that the luteal cells are derived from the follicular cells.

The glandular nature of the organ is admirably shown in the corpus luteum of *Dasyurus* (see Figs. 13 and 13a).

The yellow pigment of the corpus luteum belongs to the group of lipochromes. These are found in several organs and tissues and are related to similar vegetable pigments. The lutein from egg-yolk has a molecular weight of 624 and the formula given is $C_{40}H_{56}O_2$. It is isomeric with xanthophyll,

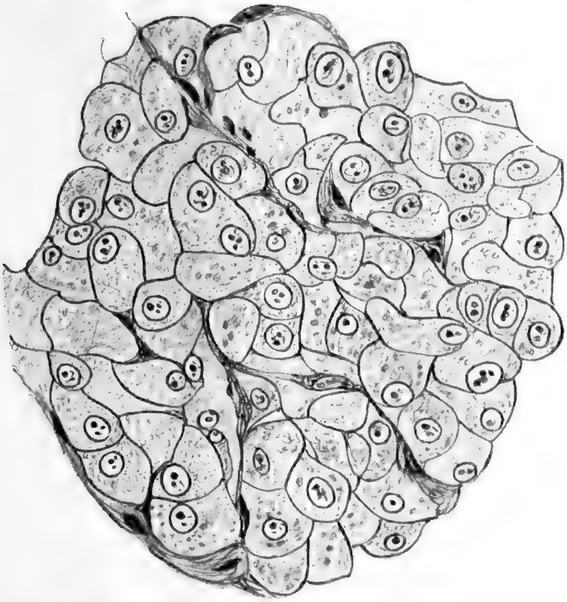


FIG. 13a.—Portion of corpus luteum of *Dasyurus* under a high power, showing the glandular nature of the constituent cells. (Drawn by Mrs. F. D. Thompson from material supplied by Prof. Charles O'Donoghue.)

obtained as a by-product in the preparation of chlorophyl. The precise chemical nature of lutein has not yet been made out, but it has been suggested that it is an oxidation product of carotin (obtained from carrots), or again, that it is an oxidation product of the esters of cholesterol with unsaturated acids.

Different "active principles" have been isolated from corpora lutea by means of different solvents. Thus some of these are extracted by ether, others by acetone. If these are to be

tested medicinally there is great need for more uniform methods in the preparation of extracts. The only definite physiological effects alleged to be produced by luteal extracts are changes in the contractions of the uterus and smooth muscle of other regions, and an effect on the flow of milk. For example, Itagaki states that luteal extracts usually increase the tone of the surviving uterus of the rat, rabbit, dog, and guinea-pig, though occasionally the result is in the opposite direction. He believes that the different results are due to the effects of two separate principles, having antagonistic actions on the uterus. The inhibitory substance is soluble in alcohol, while the augmentory principle is insoluble in alcohol, but soluble in water. The evidence for the existence of two opposing active principles cannot be regarded as very convincing. Chauffard urges that the yellow body is a centre for the production of cholesterin. He points out that this substance is present in the corpus luteum during pregnancy, and that cholesterinæmia occurs at this time. But the corpus luteum is not the only centre for the production of cholesterin. Extracts of the corpus luteum are said to stimulate the contractions of the vas deferens and the seminal vesicles, but this must be an accidental and not a specific reaction. One cannot avoid the suspicion that in such experiments no adequate regard is paid to control experiments carried out with extracts from other organs and tissues.

Ott and Scott (1910) reported that extracts of pituitary, thymus, pineal, and corpus luteum act as galactagogues. So far as the pituitary and luteal extracts are concerned, the result was confirmed by Schäfer and MacKenzie. It is now generally considered that galactagogue principles can be extracted from pituitary, corpus luteum, pineal, mammary gland, and the involuting uterus. It is very probable that the list will be extended, but there is little reason to regard all these organs as furnishing "hormones" for the purpose of stimulating milk secretion.

Corpus luteum extracts are now frequently employed by medical men in cases of deficient milk secretion in women.

Attempts to replace the internal secretion of the corpus luteum by means of injection of extracts have not given very satisfactory results. Several years ago the present writer, in conjunction with Dr. F. H. A. Marshall, performed a series

of experiments designed to test the theory that the œstrous cycle is determined by an internal secretion on the part of the ovary. Extracts were made from ovaries in a pro-œstrous or œstrous condition and injected subcutaneously into a bitch at a period as remote as possible from the œstrous one. In some of these experiments a swelling of the vulva and other slight signs of the œstrous condition were induced, but the results were not decisive enough to warrant publication. Since then, however, Marshall and Jolly have reported that "heat," or a transient condition resembling it, can be produced by the injection of extracts of œstrous ovaries. It is possible that in some of these experiments the extracted ovaries contained corpora lutea and that the effects observed (chiefly consisting of hyperæmia of the external genitals) were due to active substances derived from the yellow bodies. Recent experiments have confirmed the fact that injection of extracts of ovary cause hyperæmia and swelling of the reproductive organs. It is not clear from these experiments how far the results are due to corpus luteum and how far to other parts of the ovary. The changes induced do not seem to be true cyclic growth processes, but simply transient circulatory effects. Pearl and Surface have recently shown that the desiccated fat free substance of the corpus luteum of the cow, when injected in suspension into an actively laying fowl, immediately inhibits ovulation. After the bird begins ovulating again, the laying goes on as before. The substance which produces the effect is rendered inactive by boiling.

In future researches upon the pharmacodynamics of ovarian extracts great attention should be paid to the chemistry of the products obtained, and very careful control experiments should be carried out.

Prenant, in 1898, thought that the corpus luteum, through an internal secretion, influences the general metabolism of the body and prevents ovulation during pregnancy and between the œstrous periods. As a result of the investigations of Loeb and others, this theory seems now to be firmly established. Loeb found in sixty-six guinea-pigs that spontaneous ovulation rarely occurs within sixteen to eighteen days after a preceding ovulation. In twenty-five animals all the yellow bodies were removed and 92 per cent. of these all ovulated within 12–16½ days after coitus, showing a marked shortening of the

interval between ovulations. It is known that pregnancy will not in itself inhibit ovulation. We have seen above that the injection of luteal extracts into fowls will prevent ovulation. It is clear that the ovulation can only be accelerated up to a certain degree by removal of the luteal substance. The succeeding ovulation has to await the maturation of follicles. Without the presence of follicles in a state of maturity, renewed ovulation is impossible, even after extirpation of the corpora lutea.

The idea that the corpus luteum might be an organ with an internal secretion was first conceived by Gustav Born, who suggested that the function of the internal secretion was to subserve the fixation and development of the impregnated ovum in the uterus. Born did not publish his views, but bequeathed the idea to Fraenkel to work out. It was found by this and subsequent authors that ovariotomy (involving removal of corpora lutea) caused discontinuance of pregnancy in animals. As pointed out by Marshall, there is no evidence that the corpus luteum governs the fixation of the embryo otherwise than by stimulating the uterine mucous membrane to hypertrophy.

In rabbits spontaneous ovulation and subsequent production of corpora lutea do not occur. The additional stimulus of coition is necessary. Ancel and Bouin observed that, if the follicles be ruptured artificially, corpora lutea are formed and a growth of the mammary glands supervenes. But O'Donoghue found that rupture of the follicles was not always succeeded by the formation of corpora lutea, and when such formation did not occur, there was no growth of the mammary glands (*vide infra*, p. 88).

The changes in the uterine mucosa produced by the corpus luteum, and which help in the fixation of the fœtus, were studied in greater detail and by a new method by Loeb. It occurred to this observer that the influence exerted by the corpus luteum might be explained if experiments were conducted in which the changes in the uterus could be studied directly, without the interference of a fertilized ovum. Accordingly Loeb excluded the chance of pregnancy by tying the Fallopian tubes immediately after the occurrence of coition. Ordinary foreign bodies and various mechanical stimuli were applied to the uterine mucous membrane. It was found that when

this latter had been sensitized by the internal secretion of the corpus luteum, the mechanical stimulation gave rise to a maternal placenta—an artificial deciduoma—at the point of stimulation. The mechanical stimulus has the same or a very similar effect to that of the ovum. Even apart from special mechanical stimuli, the uterine mucosa frequently shows some slight deciduomatous growth, due in all probability to some ill-defined stimuli occurring in normal life and rendered effective by the internal secretion of the corpus luteum. O'Donoghue finds that in marsupials, in which the yellow body is persistent in the non-pregnant animal, the uterine overgrowth is specially marked. He suggests that the effect of the mechanical irritation is chiefly to localize the overgrowth, and thus produce definite deciduomata.

Loeb's observations have been confirmed by several authors.

It seems clear, then, that the internal secretion of the corpus luteum sensitizes the uterine mucous membrane and renders it capable of reacting to mechanical stimulation. There is a relation between the quantity of the internal secretion poured out by the corpus luteum and the degree of response which can be elicited by mechanical irritation. The response can only be obtained when an amount of secretion sufficient to sensitize the mucous membrane has been poured out. If the stimulus be applied when the body is just beginning to secrete, little effect may be produced. But if the stimulation is carried out later on, at a time when the uterine mucous membrane has become completely sensitized, the secretion of the substance goes on for a few more days and increases the reaction. The ovum becomes attached at about the time when the greatest sensitization of the mucosa has been obtained. The substance secreted by the yellow body is not specific, that is to say, the substance secreted by one individual will cause growth in the sensitized uterus of a second individual of the same species. The effect, however, is less pronounced than in the organism to which it belonged. This difference is supposed to be due to the presence of "homoiotoxins" in the second individual. The artificial deciduomata in any particular species have the structure of the normal maternal placenta. In some animals these are confined to the uterus, but in women deciduomata can be produced in the Fallopian

tubes, as in cases of tubal pregnancy. The readiness with which extra-uterine pregnancy may develop in any species depends, in part at least, upon the readiness with which the stroma of the host responds with the production of a decidua favourable for the development of the embryo.

It is probable, then, that the corpus luteum aids in the fixation of the embryo by favouring the growth of the deciduoma in response to the stimulus of the ovum. But recent investigations point strongly to the view that the yellow body has an important function related to the mammary gland.

It was suggested by Hildebrandt that during pregnancy an impulse is exerted by the ovum on the mammary glands, which stimulates them to growth. Lane-Claypon and Starling reported that extracts of fœtus stimulate the growth of mammary gland. But virgin animals sometimes produce milk. Hence it is clear that the source of the stimulus which normally calls forth the development of the mammary gland must be sought elsewhere than in the developing fœtus. Frank V. Unger and O'Donoghue have definitely urged that this source is to be found in the corpus luteum. The last-named author, working upon Dasyurus, has found that the enlargement of the mamma begins quite apart from fertilization, and is continued when there is no fertilized ovum present to produce an internal secretion. He gives tables and curves to show that as soon as the corpus luteum has begun to be formed, the growth of the mammary gland commences, and this growth is notably increased after the corpus luteum is fully formed. As we have seen above (p. 86) O'Donoghue observed that, if follicular rupture is not followed by formation of corpora lutea, there is no growth of the mammary glands. The conclusion can scarcely be avoided that the hormone causing the growth of the mammary gland is produced in and secreted by the corpora lutea.

Reference has already been made to the "interstitial cells" or the "interstitial gland" ("puberty gland" of Steinach). The tissue is so often referred to in the literature, that it is astonishing how little can be definitely stated about it. It is not known certainly whether the tissue is epithelial or whether it is of connective tissue origin. It is not even known whether it is constantly present. In fact, out of more than one hundred species so far examined, 50 per cent. are said to possess none.

It has been supposed that the cells undergo periodic changes of such a character that at certain times they may be more, at others less, abundant or conspicuous. For example, they are stated to reach their greatest development during pregnancy and lactation.

The cells have a typically glandular appearance. They have an abundant blood supply and contain granules. These are of various kinds, as indicated by their staining reactions. There is an abundant chondrioma and enclosures of a lipoid character, siderophil protoplasm, and distinctly polychromatic, large, round nuclei. The chondrioma is made up of chondrioconta and mitochondria. It undergoes important modifications in the course of the evolution of the cell. The granulations, at first few, increase in number in the later stages ; the fatty products are the result of a chemical change in the mitochondrial substance. The lipoid enclosures probably represent the products of secretion (Athias).

When the theory of internal secretion on the part of the ovary had once become generally accepted, and when the organ was found to contain, in addition to the follicles, certain other cells of a glandular appearance, it was natural that these last should be charged with the function of internal secretion. But so far no hypothesis in regard to them has been put forward which has much direct evidence in its favour. Perhaps the best accredited of such hypotheses is that the interstitial cells preside over the nutrition of the reproductive organs (e.g., the uterus) and are responsible for the appearance of the secondary sexual characters.

In birds there seems to be some doubt whether the "interstitial" cells can be regarded as secretory elements. They appear to contain hæmopœetic centres.

Bell urges that "femininity" is dependent, not only on influences arising from the ovary, but on all the various internal secretions. The relations of the thyroid gland and the adrenal to the female reproductive system are treated in other chapters (pp. 241, 400). The pineal is alleged to have an influence on sexual precocity (p. 390). It is believed that the pituitary and the thymus influence the metabolic functions, determining the onset of puberty. The question is rendered complicated by the influence of the various internally secreting organs upon each other (p. 395).

D. Ovarian Medication.

Brown-Séquard in a first communication to the Société de Biologie, in June, 1889, expressed the opinion that the ovaries of animals might furnish a juice which would have a beneficial effect upon women similar to that obtained in the case of men by the employment of testicular extracts. In 1890 he reports that a Parisian midwife had injected herself with a liquid made from the ovaries of guinea-pigs, and had benefited thereby. He further calls attention to a report of Villeneuve, who made injections of ovarian extract into three individuals—two women and one man. One of the women, who had undergone double ovariotomy, was very considerably benefited. Finally, he gives an account of the work of an American lady doctor, Mme. Augusta Brown, who "avec un grand courage" had observed good results by injection of extracts made from the ovaries of rabbits. The injections were mostly subcutaneous, but the application was sometimes made on to the skin after blistering, and in one case the juice was applied directly to the uterus (in the case of prolapse).

Brown-Séquard does not seem to regard these reports as of much value, for he concludes that it is the testicular juice which ought always to be given "comme agent dynamogénique" in women as well as in men. He states that the ovarian extracts are less powerful than the testicular, and their action is not specific.

Mainzer obtained good results in the treatment of heats, sweating, headache, etc., after double ovariotomy, and also in the vasomotor troubles of the menopause.

Bestion de Camboulas gives many interesting references showing how completely persuaded were many physicians of the period that the ovary is a gland with an internal secretion. The evidence at their disposal was, however, very meagre. They seem to have been led to their belief chiefly by Brown-Séquard's famous dictum that all glands, whether or not they possess a duct, pour into the blood useful principles, whose absence makes itself felt after their extirpation or their destruction by disease.[1]

Bestion de Camboulas gives an account of the various

[1] Bestion de Camboulas says naïvely: "The ovary, being a gland, ought not to escape this law."

modes of preparing ovarian extracts. He employed (1) fresh gland, (2) dried gland, (3) ovarian juice or fluid extract. This last was watery or alcoholic, or a glycerin extract. He recommended the employment for medical purposes of the ovaries of the sow.

This author performed a series of experiments upon animals in order to investigate the toxicity of the ovarian extracts, and found that the glycerin or watery preparation is much more toxic for the male than for the female. After large doses males died with pyrexia, hæmaturia, and other disturbances. With non-toxic doses the males lost weight, the females gained weight. The resistance of pregnant females was much less than that of non-pregnant.

Clinically, his results were as follows: Troubles of the menopause, natural or after castration, are considerably relieved by ovarian extract without other medication. There is constant amelioration in cases of amenorrhœa and chlorosis, and there is a real improvement in the mental troubles which accompany genital lesions, or which occur after castration. Improvement in the general condition is marked in all cases. The extract should never be given to pregnant women.

Andrews speaks very cautiously as to the benefit accruing from the administration of ovarian extracts, while Cohn finds that the results are nearly always disappointing.

Batty Shaw says that the special value of ovarian substance is shown in cases in which the ovaries are ill-developed, or have become atrophied as at the menopause, or have been removed by operation.

There are numerous other papers on the subject of ovarian medication. Much of the work has been very uncritical. No due regard has ever yet been taken even in experiments on animals as to the condition of the ovary from which the extract is made, and it seems clear that the corpus luteum will in the future have to be considered separately both experimentally and clinically.[1]

[1] Bouin and Ancel now believe that the corpus luteum secretes a hormone which excites the mammary gland to growth, but that the hormone which excites to secretion is derived from a gland which they claim to have discovered in the muscular layer of the uterus, and to which they have given the name "myometrial gland." Recent work has thrown considerable doubt upon the existence of any such "gland" in the uterine wall.

E. Osteomalacia

Perhaps this is the most suitable place in which to refer to the disease known as osteomalacia. The theory which connects this condition with hyperfunction of the ovaries has found most adherents. The argument in favour of this view is largely based upon the fact that the condition is benefited both by removal of the ovaries and by artificially induced labour.

CHAPTER XI

THE INTERNAL SECRETION OF THE ADRENAL BODIES

(The Cortex of the Adrenal and the Chromaphil Tissues)

A. Introductory

When we consider the extraordinarily voluminous literature devoted to the adrenal bodies, and the immense amount of time and patience which has been expended by physiologists, pathologists, and comparative anatomists, in the attempt to elucidate their function, it is regrettable to have to admit that we are still unable to give a satisfactory answer to the question, "What is the function of these bodies?" We have, perhaps, a fairly reasonable suggestion to offer as to the service in the economy rendered by the chromaphil tissues (including what in mammals is called the "medulla" of the adrenal), but of the physiology of the "cortex" we still know very little.

There are two important discoveries which stand out among all others as epoch-making. The first is the observation by Addison in 1849 that certain cases of disease characterized by pigmentation of the skin, languor, and other symptoms, are associated with destructive lesions—usually tubercular—of the adrenal bodies. The second is the discovery in 1894 by Oliver and Schäfer of the blood-pressure-raising activity of extracts of the medullary portion of the gland. We are, however, by no means clear, as will be seen in the sequel, what is the precise relationship between the facts revealed in these two discoveries.

A third very important step in our progress ought to be referred to in this place. This is the isolation in crystalline form of the active principle of the medulla of the gland (*i.e.*, of the chromaphil tissues) by Takamine and Aldrich independently in the year 1901.

The first definite account of the adrenals with illustrations

is given by Eustachius in 1563. For a long time the discovery was unnoticed, or the existence of the new organ was denied! It is indeed remarkable, as pointed out by Biedl, that Vesalius in 1642, Fallopius in 1606, and Fabricius in 1738 make no reference to the bodies discovered by Eustachius. However, they began to be referred to even before the end of the sixteenth century in the medical books as the "glandulæ" or the "capsulæ renales Eustachii."

The story of Montesquieu's participation in the history of our subject is so interesting that, although it has now been told several times, it will well bear repeating.

In the year 1716 the Academy of Sciences of Bordeaux offered as the subject of a prize essay, "What is the Use of the Suprarenal Glands?" The essays submitted were placed in the hands of Montesquieu, the famous author of the *Esprit des Lois*, who acted as judge. His report is of especial interest, not only because of the personal fame of the author, but because it gives an admirable critical account of the older views upon the adrenal bodies. The style is satirical, but it is probable that it was not intended to be so satirical as it appears to us at this date, when every theory mentioned in 1716 appears to us positively absurd. Montesquieu briefly discusses the older views that the glands, serve to hold up the stomach and strengthen the nervous plexus which touches them, or that "black bile" is preserved within their cavity (Bartholin), or that they serve to collect the humidities which leak out of the great vessels in the neighbourhood. He then criticizes the essays which were presented to the Bordeaux Academy.

"We have found one author who declares that there are two kinds of bile: one grosser, which is separated out in the liver; the other more subtle, secreted in the kidneys by the assistance of the ferment which flows from the suprarenal capsules by ducts of which we are ignorant, and of which," comments Montesquieu, "we are menaced with perpetual ignorance."

"Another describes to us two small canals which carry the liquids from the cavity of the capsule into the vein belonging to it; this humour, which many experiments lead us to consider alkaline, serves to give fluidity to the blood returning from the kidneys after it has been deprived of serosity in the formation of the urine.

"Another essayist, who gives a difference between conglobate and conglomerate glands, has placed the suprarenal glands among the conglobate. In his opinion they are nothing but a continuity of bloodvessels within which, just as in filters, the blood becomes more subtle. . . . In these glands, as in all the conglobate glands, no excretory duct exists, because there is no question of the secretion of liquids, but only of making them more subtle."

In conclusion, Montesquieu announces that the Academy will not award its prize this year, since the object of the offer has not been achieved. He ventures his own opinion that "le hasard fera peut-être quelque jour ce que tous ses soins n'ont pu faire," and he is polite enough to state! "Mais ces efforts impuissants sont plutôt une preuve de l'obscurité de la matière que de la stérilité de ceux qui l'ont traitée." [1]

In attempting to assign a function to the adrenal bodies, it is essential to bear in mind their dual nature. As we shall see later, the adrenal body of the higher animals has been derived from two separate and distinct kinds of tissue in lower vertebrates; and although there is a more or less gradually increasing tendency for the two tissues to become united as we ascend the scale, yet it is only in mammals that the terms "adrenal cortex" and adrenal medulla" are strictly appropriate.

It is essential that, before dealing with the physiology of the adrenals, we should give some account of their comparative anatomy and development.

B. Comparative Anatomy of the Adrenal Bodies

1. *Introductory*

It is only in the Amniota that we find a definite organ whose parenchyma is divided into two distinct portions, whose cellular constituents are quite different in character from each other.

In the Anamnia we have the organ represented by a number of small bodies. The Amphibians in some respects occupy an intermediate position. In Pisces and Cyclostomata we find two distinct categories of bodies each consisting of a special

[1] The above account is largely taken from Biedl.

form of cell, which categories are homologous with the two constituents of the adrenals of higher vertebrates.

In Amphioxus nothing corresponding to the adrenals has so far been discovered, and in the Invertebrata the matter may perhaps be considered somewhat doubtful.

2. *Invertebrata*

Leydig discusses the possibility of the existence in some Invertebrata of the equivalents of the adrenal bodies.

Some years ago the present writer had considered the possibility of the existence of the representatives of cortex and medulla of the adrenal bodies in the Invertebrata, but had not succeeded in finding any organs or tissues which seemed at all likely to correspond to them. But just previously to that time physiological research had rendered it possible to test any unknown organ or tissue to see if it should be homologous with adrenal medulla. An extract made from the medulla of the adrenal or from any (chromaphil) tissue of the same nature possesses powerful pressor properties.

Accordingly an extract from certain tissues (including the cells which Leydig thought might correspond to the adrenal bodies of vertebrates) of *Paludina vivipara* was prepared and injected into the venous system of a cat. The result was negative, possibly because the material necessarily contained so much nervous tissue which would tend to lower the blood-pressure. Cleghorn finds that glycerin and saline extracts of sympathetic ganglia produce a fall of blood-pressure, in spite of the presence in these ganglia of chromaphil cells like those in the medulla of the adrenal body.[1] It appears, also, that it is impossible to obtain any rise of blood-pressure by injecting extracts of carotid glands into an animal, because there is so much admixture with various tissues whose extracts have a depressor effect.

Poll and Summer describe certain cells in the abdominal ganglia of *Hirudo medicinalis* which stain a yellowish-brown with Müller's fluid. They consider it probable that these are homologous with the chromaphil cells discovered by Stilling.

[1] Cleghorn did not ascertain that this result might be obtained from any nervous tissue, whether brain, spinal cord, or peripheral nerve; in fact, he states that this is not the case.

Such cells were later described in a large number of leeches—Gnathobdellidæ and Rhynchobdellidæ—and still later Poll gives a description and some very convincing drawings of these chromaphil cells in *Nephthys scolopendroides*. As regards the yellow cells of Pontobdella described by Leydig, these appear to be of a different nature. As pointed out by Poll, we are sadly in need of another micro-chemical test for adrenin-containing tissues. If the ferric-chloride reaction could be used for histological purposes, it would clear up many doubtful points.

Roaf and Nierenstein have expressed their belief that there is a substance in the hypobranchial gland of *Purpura lapillus* which is allied chemically and physiologically to adrenin. But the identity of the substance with adrenin has been denied. Roaf has recently returned to the subject and finds that in *Purpura lapillus* there are associated (1) a pressor substance in the strip of tissue adjacent to the so-called rectal gland; (2) a purple-forming material in the same area; (3) a collection of bichromate-reacting granules also in the same situation. The inference is that these, if not identical, are at least functionally associated.

It is curious that, so far as I can ascertain, Poll and Roaf make no reference to each other's work. It is clear that the structures they respectively describe are quite different from one another. The tissue described by Roaf is not apparently connected with the nervous system, while the chromaphil cells of vertebrates are always intimately related to the sympathetic. The cells described by Poll are, on the other hand, within the central nervous system, and, at any rate, bear a very great resemblance to the cells which are familiar to us in the vertebrate sympathetic.

Further investigations on the chromaphil tissue of annelids have been carried out by Biedl and by Gaskell. Both these authors claim that they have succeeded in bringing about inhibition of the virgin uterus of the cat by means of an extract of the ganglia of *Hirudo medicinalis*. The cells described by Gaskell are nerve-cells which give a chromaphil reaction and which he thinks are the common ancestors of both the chromaphil and the sympathetic systems of vertebrates. This is not in accordance with the views of Giacomini.

3. *Anamnia*

In the Clyclostomata, the lowest vertebrates in which adrenal elements are certainly known to exist, our knowledge is confined to the Petromyzonta and Bdellostoma.

In Petromyzon [Giacomini] there are two distinct series of bodies. One of these is represented by small, irregular, lobulated structures in the wall of the posterior cardinal veins and the renal arteries, and of arteries dorsal to the kidney. They project into the lumen of the vessels, and consist of cylindrical or polyhedral cells, containing granules which stain black with osmic acid. These are the cortical or inter-renal bodies. The other series, or the chromaphil series, extends from the region of the second gill cleft to the tail of the animal. The bodies of this series are thin strips of tissue running along the large arteries and their branches. These bear the same relations to the veins as the cortical bodies.

This distribution of the chrome staining tissue in *P. fluviatilis* has recently been confirmed by J. F. Gaskell. Extracts of the regions in which this tissue lies, *viz.*, the walls of the aorta and cardinal veins and the sinus region of the heart, cause a rise of blood-pressure in the cat.[1]

In Bdellostoma the chromaphil cells have been observed, but not the inter-renal or cortical.

The relationships of the two adrenal representatives in Elasmobranchs were first suggested by Balfour in 1878. He called the representative of the cortex the "inter-renal," while what we now know as the "chromaphil corpuscles" (representing the medulla of the adrenals of higher vertebrata) he called "suprarenal bodies." That the paired "suprarenal bodies" of Balfour really correspond to the medulla of the mammalian organ was first definitely shown by the present writer by the physiological test. This was fully confirmed by the chemical test [Moore and Vincent]; and that the "inter-renal" of Balfour is really homologous with the cortex of the mammalian body was rendered clear from the negative physio-

[1] The present writer, working in conjunction with Mr. W. E. Collinge, made an attempt some years ago to find the adrenals in Cyclostomata, but we considered that there was no satisfactory evidence to show that the bodies described by Rathke, Müller, and others had anything to do with the adrenals.

logical and chemical tests, and from careful histological comparisons.

The paired "suprarenal bodies" (chromaphil) are situated on branches of the aorta, segmentally arranged, and extend on each side of the vertebral column from the front part of the sinus of Monro to the posterior end of the kidney. The anterior pair are elongated, and correspond usually to three or four segments. These bodies are in close relation to the ganglia of the sympathetic chain, and contain large numbers of chromaphil cells, though they appear not to be made up entirely of them. (Figs. 14, 15 and 22.)

The inter-renal body [Figs. 14 and 15 (*i.r.*)] is an "ochre-yellow" rod-shaped structure, paired in the rays, unpaired in the dogfishes and sharks, lying usually in the region of the posterior part of the kidney, but sometimes extending as far forward as the anterior extremity. It bears a striking resemblance in its colour, general appearance, and relations to the kidney, to the adrenals of the Anura, and in the first two of these features to those of the Reptilia. The body consists of cells which have the same general appearance and the same micro-chemical reaction as the "corpuscles of Stannius" (the cortical adrenals of Teleostean fishes), and the cortex of the adrenals of higher vertebrates. (See Fig. 21.)

The effect of injection into the venous system of a mammal extract made from the "paired bodies" of Elasmobranchs is shown in Fig. 16. It will be seen that there is a very marked rise of the arterial blood-pressure. In Fig. 17 is seen the effect of the injection of an extract made from the inter-renal. There is a certain effect upon the blood-pressure which can be readily explained as the result of more or less admixture with "medullary glands" in making the extract.

In Teleosts the cortical adrenal bodies are usually paired, round or oval, pale pink bodies, placed on the spinal or ventral surface of the kidney. They are near the posterior extremity of the renal mass, and are either free on its surface or more or less embedded in its substance (Figs. 18–20). The constituent cells are of the same character, and have the same arrangement as those of the inter-renal of Elasmobranchs (Figs. 23, 24) It is now fully ascertained that these structures (the "corpuscles of Stannius") in Teleosts represent the inter-renal of Elasmobranchs. It had been erroneously considered by some authors

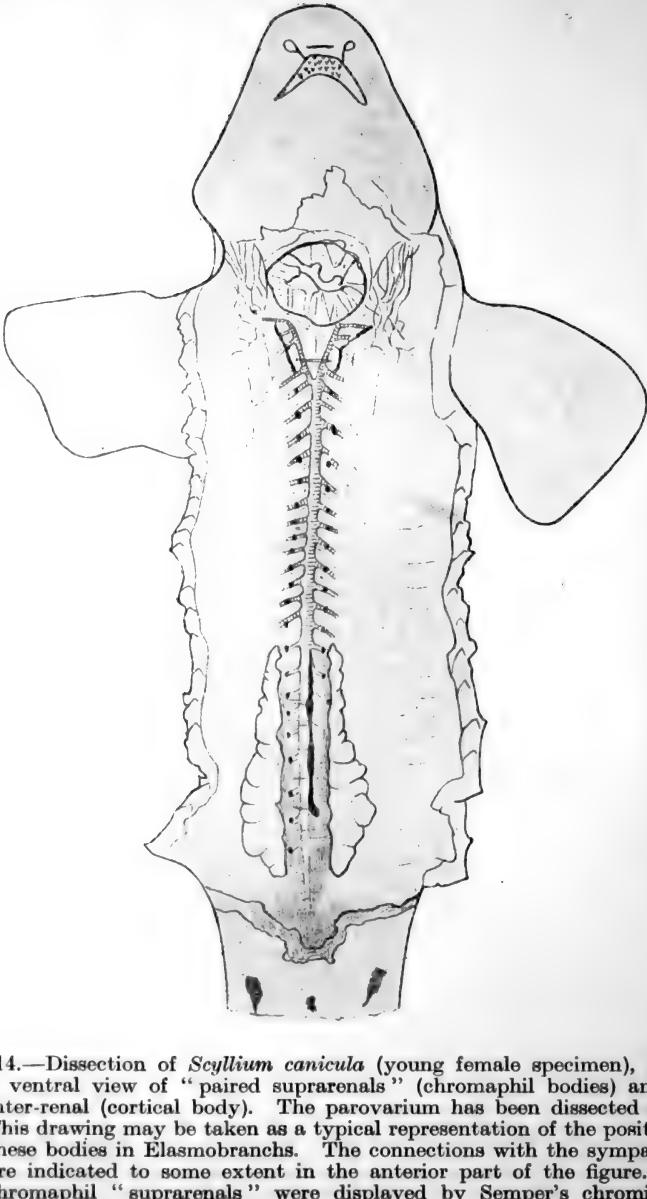


FIG. 14.—Dissection of *Scyllium canicula* (young female specimen), giving a ventral view of "paired suprarenals" (chromaphil bodies) and the inter-renal (cortical body). The parovarium has been dissected away. This drawing may be taken as a typical representation of the position of these bodies in Elasmobranchs. The connections with the sympathetic are indicated to some extent in the anterior part of the figure. The chromaphil "suprarenals" were displayed by Semper's chromic-acid method.

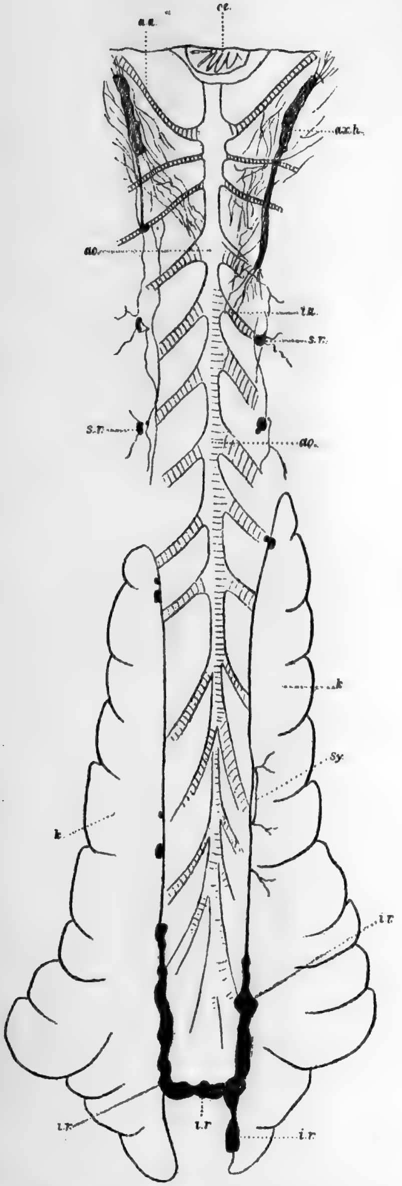


FIG. 15.—Ventral view of kidneys, etc., of *Raja batis*. This drawing represents a not unusual condition in the rays, in which there is bridge-like communication between the inter-renals of the two sides. The sympathetic is shown to some extent to about the middle of the left kidney.

Lettering common to Figs. 15, 18, 19—*a.a.*, axillary artery; *a.i.r.*, anterior broken-off portions of the inter-renal body; *ao.*, aorta; *ax.h.*, anterior pair of suprarenal bodies; *h.k.*, head kidney; *i.a.*, intercostal arteries; *i.r.*, inter-renal body; *k.*, kidney; *l.k.*, lobe of kidney substance; *œ.*, œsophagus cut across; *s.r.*, suprarenal bodies; *sy.*, main chain of the sympathetic; *sy. g.*, sympathetic ganglion; *sy. pl.*, sympathetic plexus.

that the modified pronephros of Teleosts represents the adrenal body in these fishes.[1]

[1] Since this view has now been completely abandoned, there is no need to

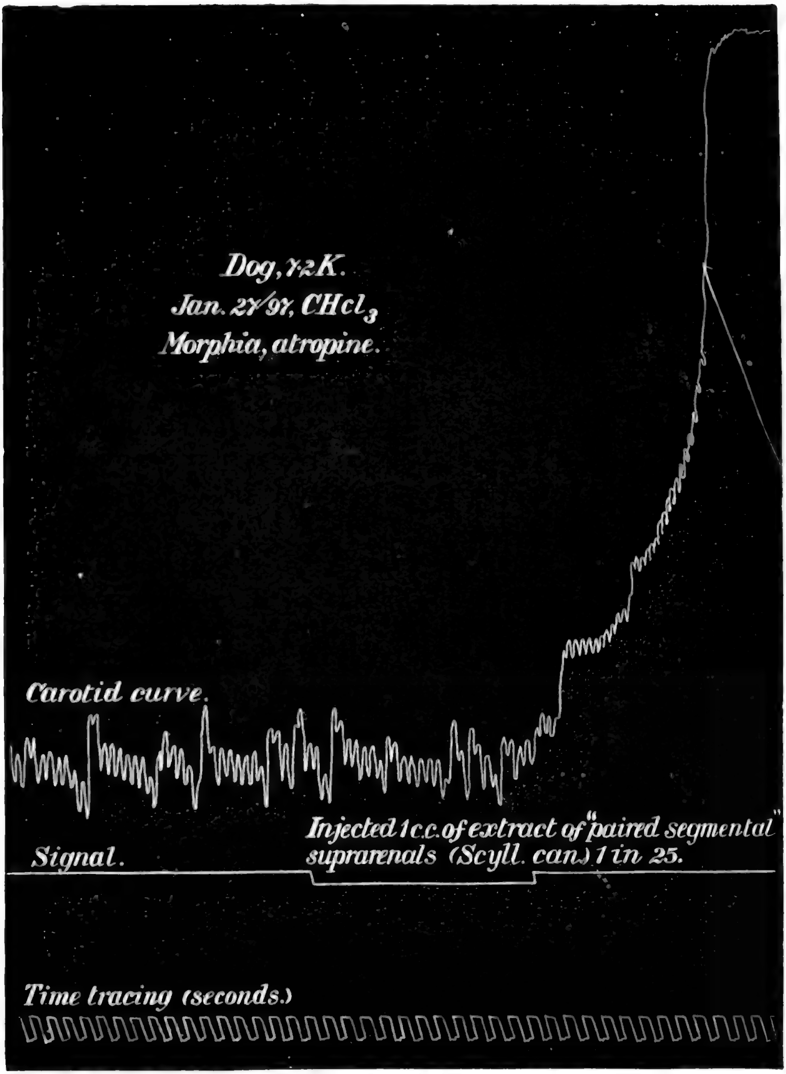


FIG. 16.—Effect of injection of 1 c.c. of extract of "paired segmental supra-renals" (1 in 25) taken from *Scyllium canicula*. It will be seen that the rise of blood-pressure is very striking.

A very important discovery has recently been made by Giacomini, who finds that the corpuscles of Stannius are not

revive the controversy. It was Rathke who first put forward this theory, which was later revived by Weldon. The view was proved to be untenable by the present writer in 1895.

the only representatives of cortical adrenal substance in teleostean fishes. He has worked out the subject especially in many fishes of the eel tribe, and finds isolated bodies on the cranial border of the "head kidney," on the anterior and

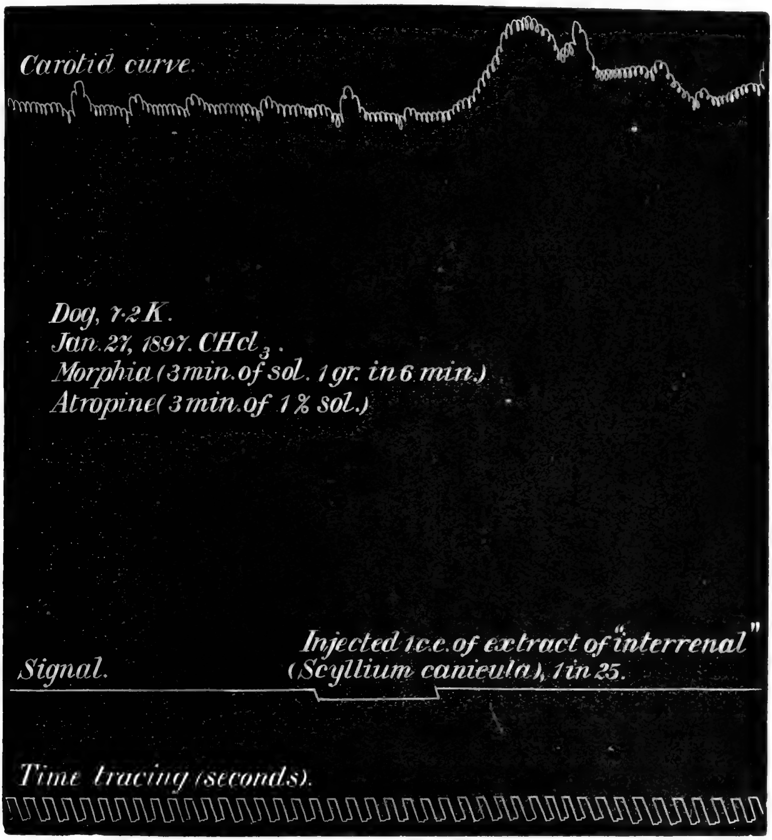


FIG. 17.—Effect of injections of 1 c.c. of extract of "inter-renal" (1 in 25) taken from *Scyllium canicula.* It will be seen that there is a certain small rise of the arterial blood-pressure. This is not at all comparable with that produced by an extract of the "paired bodies" (see Fig. 16), and is to be explained by the fact that in extracting the inter-renal from the body, it is almost impossible to avoid removal also of some of the "paired bodies."

posterior cardinal veins, which he considers are to be regarded as of the same general nature as the corpuscles of Stannius, though they present certain slight differences (Figs. 20 and 24).

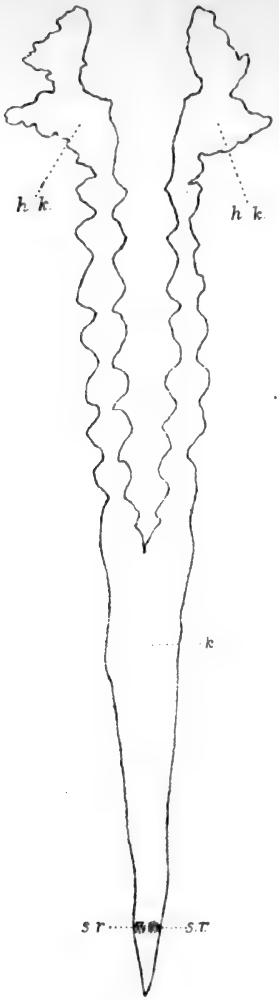


Fig. 18.—Kidneys and cortical adrenals (corpuscles of Stannius) of *Pagellus centrodontus*. The adrenals are on the spinal surface, shown by the dotted lines.

Lettering same as for Fig. 15.

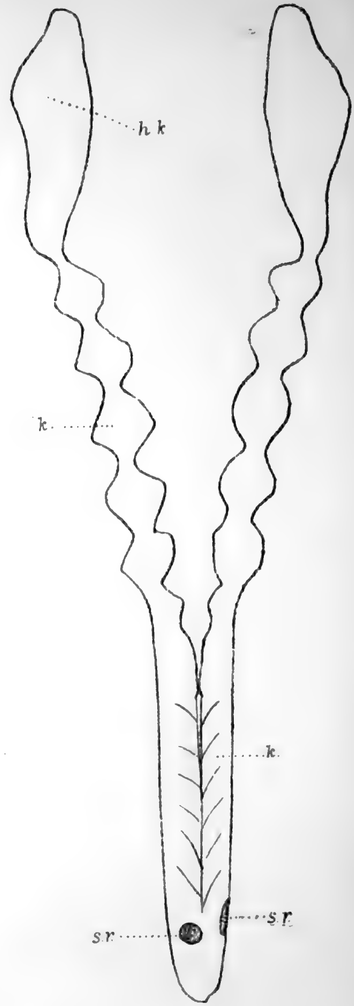


Fig. 19.—Kidneys and cortical adrenals (corpuscles of Stannius) of *Gadus morrhua* (ventral view). One body is on the ventral surface, the other half-way round towards the spinal surface.

Lettering same as for Fig. 15.

So that in teleostean fishes we have now to consider a "cranial" and a "caudal" cortical body. This is of the greatest

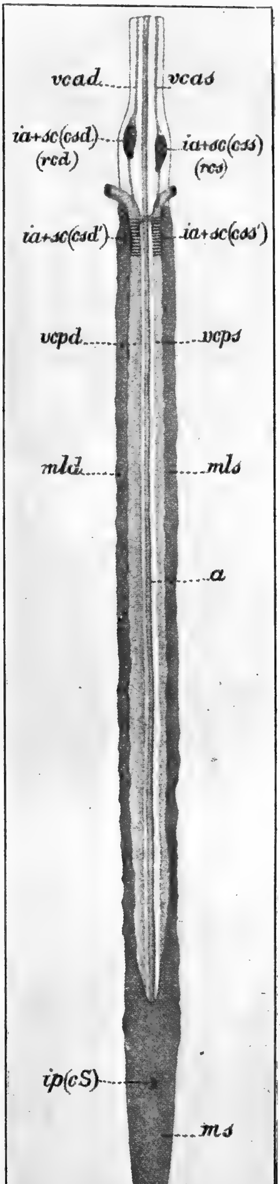


FIG. 20.—Semi-diagrammatic figure showing the kidneys and their relations with the cardinal veins and the cortical and chromaphil tissues in an adult *Conger vulgaris*. The parts indicated by a series of horizontal parallel lines show where one finds cortical and chromaphil tissues intimately associated. *a*, aorta; *ia* + *sc* (*csd*) (*rcd*) cortical and chromaphil substance ("suprarenal capsule") contained in the right head-kidney; *ia* + *sc* (*css*) (*rcs*) do. in left head-kidney; *ia* + *sc* (*csd*[1]) cortical and chromaphil substance ("suprarenal capsule") contained in the cranial portion of the right vena cardinalis posterior; *ia* + *sc* (*css*[1]) do. in left side; *ip* (*cs*), posterior cortical body ("corpuscle of stannius"); *mu*, *mls*, lymphoid masses right and left; *ms*, caudal active portion of kidney (mesonephros); *vcpd*, *vcps*, post, card. veins R. and L.; *vcad*, *vcas*, primitive ant. card. veins, R. and L. (From Giacomini.)

importance as bearing upon certain experimental investigations (*vide infra*, p. 152).[1]

To Giacomini also belongs the credit of having discovered the chromaphil or medullary structures in teleostean fishes. They consist of cells which stain brown with salts of chromium in the walls of the cardinal veins, especially on the right side and towards the cranial end of the body, along the lymphoid

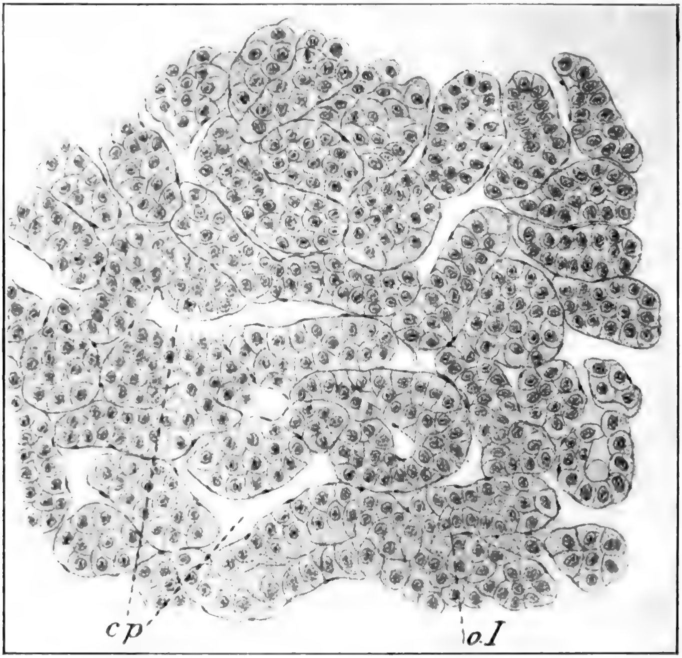


FIG. 21.—Transverse section of the Inter-renal body of *Trigon violaceus* (from Diamare).

tissue of the head kidney. The groups of cells are disposed between the lobes of the cranial cortical body. These had often been searched for by previous observers, but in vain.

In Ganoids the cortical representatives were noted by Stannius in 1846. He describes them as small whitish or yellowish bodies scattered throughout the substance of the

[1] Giacomini has more recently expressed the opinion that the corpuscles of Stannius are not homologous with the cortical bodies of petromyzon, the elasmobranchs, and higher vertebrates. Their origin, structure, and function put them in a separate category.

kidney and forming alveoli, whose cells stain black with osmic acid (see Fig. 25). Quite recently Giacomini has described chromaphil elements in the walls of the cardinal veins and the venae renales revehentes.

The question as to the existence of adrenal bodies in the Dipnoi has long been under discussion. In *Protopterus*

FIG. 22.—Transverse section through one of the paired bodies of Torpedo (from Kohn).

annectens Parker describes "around the kidney, but more particularly along its dorsal and outer sides, masses of brown cells, which in appearance remind one of the adrenal bodies of Amphibia," and he suggests the inquiry "whether they or the lymphoid cells which give rise to them have anything to do with the adrenals." In 1895 the present writer examined this point with some care, and came to the conclusion that this

tissue—a large-celled adenoid tissue—has nothing to do with the adrenal bodies, and this notwithstanding that in some regions it has a very "epithelial," a very "glandular," appearance.

Giacomini claims to have discovered the true chromaphil bodies arranged segmentally round the intercostal arteries and

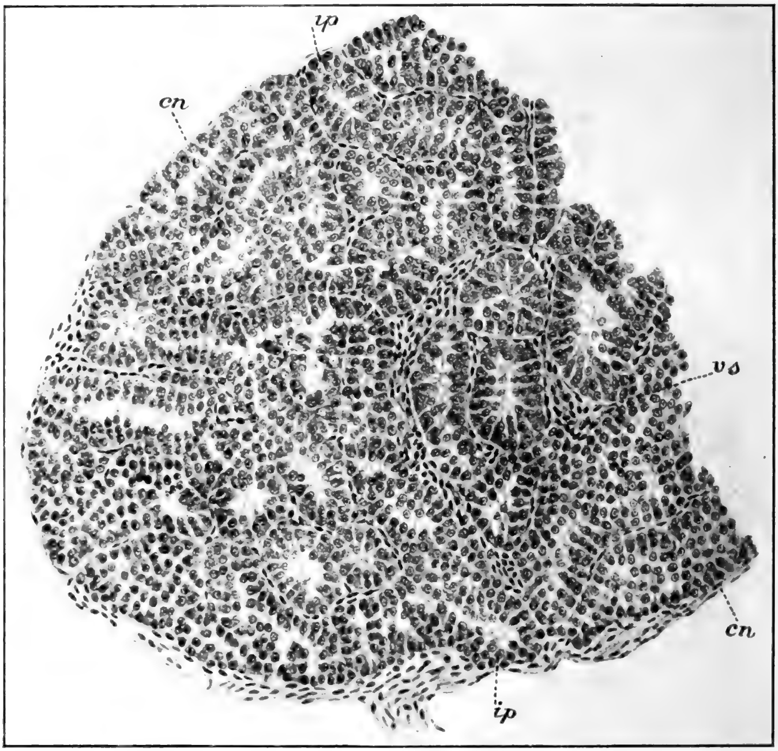


Fig. 23.—Transverse section of a "corpuscle of Stannius" (posterior inter-renal) of *Salmo fario* (from Giacomini).

in the wall of the cranial part of the posterior cardinal vein and the vena azygos dextra. He believes that the inter-renal body (cortical representative of the adrenal) is absent in this species of the Dipnoi, and renews Parker's suggestion that it may be replaced functionally by the adenoid tissue.

It seems extraordinary that there should be no representative of the adrenal cortex in the Dipnoi. The present writer has

from time to time dissected specimens of Protopterus, and has examined series of sections of this fish and of Lepidosiren, but has never been able to detect any organ or tissue which seemed likely to correspond to adrenal cortex. If the tissue originally described by Parker is in reality adenoid tissue, we should

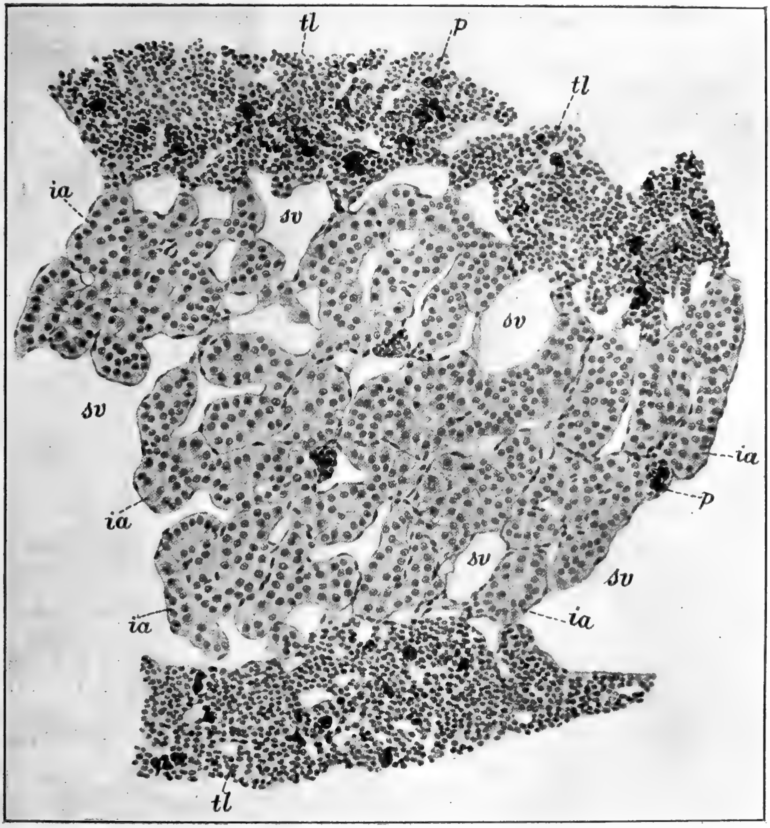


FIG. 24.—Section of head kidney of *Salmo fario* showing an islet of cortical adrenal tissue (anterior inter-renal) (from Giacomini).

hesitate to ascribe to it any secretory function. The perirenal tissue is, however, very extraordinary in appearance, and deserves careful consideration.

It is obvious that the subject of the adrenal bodies in the Dipnoi demands further investigation.

The adrenals of Amphibians are intermediate in many

respects between those of higher and lower vertebrates. In the Anura the adrenals are golden-yellow streaks on the ventral surface of the kidney, of about 15 millimetres in length in the frog to about 28 millimetres in a good-sized toad. Their width varies in a similar manner from 1 to about 3 millimetres. But their dimensions vary very considerably according to the size and development of the particular individual.

In a good specimen the adrenals present a beautiful appearance, forming on each side a series of irregular arcs with their convexity outwards, and varying in width from place to place. Their colour is a bright golden yellow, of a somewhat fatty

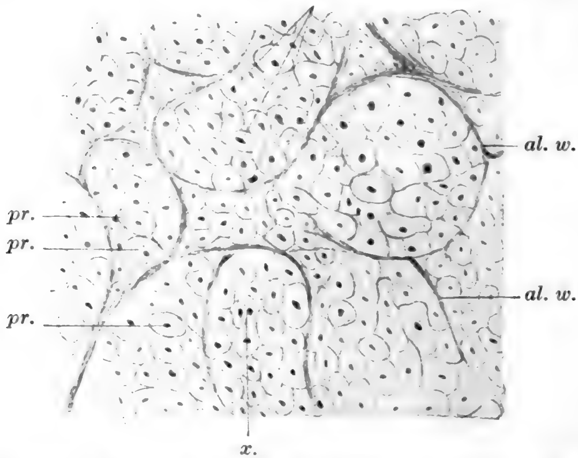


FIG. 25.—Section of an adrenal body (corpuscle of Stannius) of the sturgeon (*Acipenser sturio*). The "alveolar" arrangement is well seen, and the cell outlines are distinct.
al. w., walls of "alveoli"; *x.*, nuclei; *pr.*, granular protoplasm.

aspect, and their surface is marbled with veins. In both frogs and toads, although the body reaches nearly to the anterior end of the kidney, it always ceases at a point anterior to the posterior fifth of the organ.

In the Urodela the adrenal is broken up into a series of strips and islets which extend not only the whole length of the kidney, but also anteriorly to that organ, as far forwards as the origin of the subclavian artery.

The microscopic structure is practically the same in Anura and Urodela. The gland is seen at once to consist of two distinct kinds of structure. The greater part is made up of

cell columns, which are of varying size and shape, and which interlace in all directions. The cells are of different shapes but mostly elongated and tapering, and they contain a large round nucleus, which stains very deeply with hæmatoxylin. This structure is the "cortical," which corresponds to the "inter-renal" of Elasmobranchs, the corpuscles of Stannius ("cranial" and "caudal" series) of Teleosts and the cortex of Mammalian adrenal (see Fig. 26 s.c.).

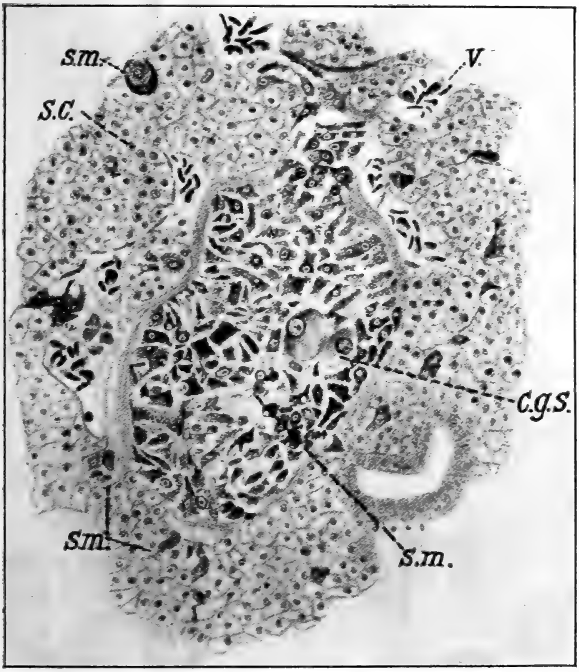


FIG. 26.—Section through suprarenal body of *Bufo vulgaris* showing a mass of medullary substance (chromaphil tissue) surrounded by cortical substance (from Giacomini).

But in addition to the above-described structure, we get masses of a different kind of cell. These are often at the borders or ends of the cell columns, but are otherwise irregularly distributed. In the islets anterior to the kidney in the Urodela these masses of cells are more numerous, and some of the islets are made up entirely of them. This structure is analogous to the paired suprarenal bodies of the Elasmobranch fishes and

the "medulla" of the adrenals of higher vertebrates. It consists of chromaphil cells. Thus in the Amphibia we have transition stages between the single adrenal of higher vertebrates and the total separation of the two constituents in the Elasmobranch fishes (see Fig. 26 s.m., c.g.s.).

4. *Amniota*

In reptiles the "cortical" and "medullary" constituents enter into closer relationship with each other than in lower vertebrates. In some groups the chromaphil cells are arranged mostly on the dorsal aspect of the gland, and only penetrate to a small extent; in others there is a considerable mixture of the two elements. In the Crocodilia and the Chelonia, for example, the relations of "cortex" and "medulla" are often almost identical with those of birds (*q. v.*).

A typical representation of the microscopical appearances of the reptilian adrenal is given in Fig. 27.

Birds show an intimate interlacement of the "Hauptstränge" (cortical) and the "Zwischenstränge" or "Intermediärstränge" (medullary), so that the latter occupy the meshes of the former (see Fig. 28).

Mammals, alone among animals, possess a true cortex and a true medulla, the latter as a rule completely surrounded by the former.

The cortex has in all essential points the same structure as its homologues in the lower vertebrates—viz., the Hauptstränge of birds, the "cortical" columns of Reptiles and Amphibians, the corpuscles of Stannius of Teleosts, and the inter-renal" of Elasmobranchs. It consists of rounded groups or columns of cells with one or two vesicular nuclei, and containing glistening fat-like granules. These granules become blackened by osmic acid, and stain deeply with Sudan III. and Scharlach R. They are dissolved by xylol, chloroform, etc., and so, when these reagents are used in the preparation of microscopical specimens, a vacuolated appearance of the protoplasm results.

The structure of the medulla is not so easy either to discover or to describe, but we may say in general terms that it consists of cell columns which are not so distinctly marked as those of the cortex. The cell outlines are not so distinct as those of the cortex, and the granules in the protoplasm have a great

affinity for nuclear stains such as hæmatoxylin, safranin, etc. These granules also reduce chloride of gold and become green in contact with ferric chloride. But their most characteristic reaction is with chromium salts. In the presence of any of these, or of chromic acid itself (in many instances, at any rate),

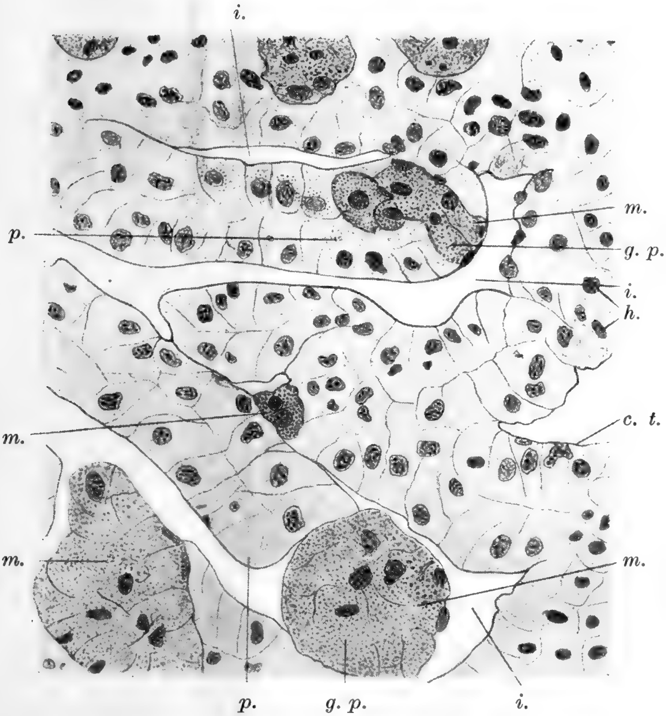


FIG. 27.—Small portion of adrenal of *Uromastix Hardwickii*. Leitz pantachrom. ; 3.0 mm. Drawn with Abbe's camera lucida. *c.*, cortex ; *c.t.*, connective tissue ; *g.p.*, granular protoplasm of medullary cells ; *i.*, interspaces between cell columns ; *m.*, medulla ; *p.*, protoplasm of cortical cells.

the cells become stained so as to assume any tint between a bright yellow and a dark brown. This reaction was discovered by Henle in the year 1865. Stilling, who discovered the cells having the same reaction along the sympathetic and in the carotid gland of mammals, called them, the corpuscles which they formed, and the medulla of the adrenal, "chromophil."

The modification "chromaphil" will be used throughout.[1]

5. *Accessory Adrenals.*

Many important points in the comparative anatomy of the adrenals may be conveniently dealt with under this heading.

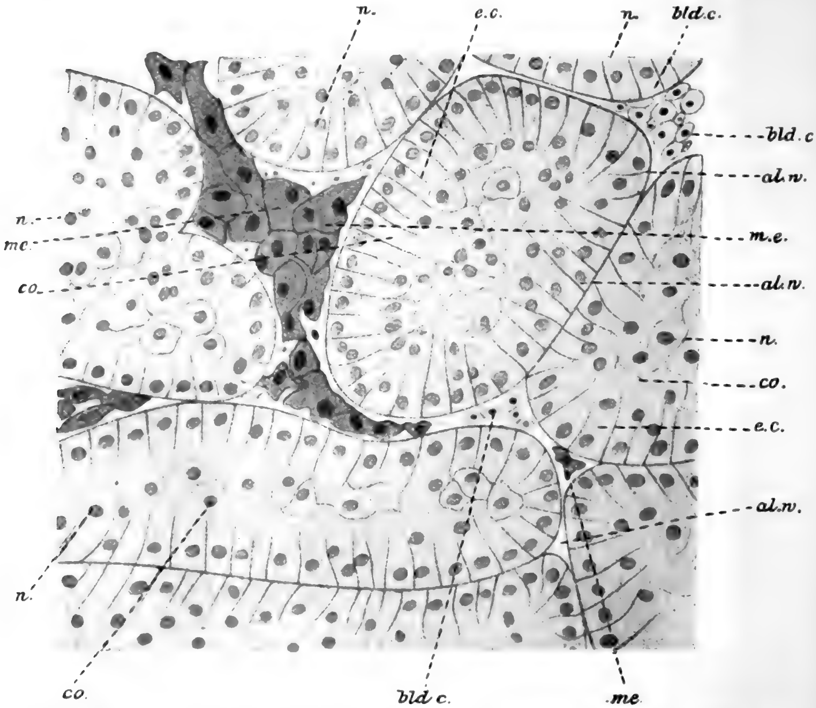


FIG. 28.—Section of the adrenal of *Meleagris Gallopavo*. The material was fixed in Müller's fluid with acetic acid and stained with hæmatoxylin. A strand of medullary cells is seen running between the cortical columns. *al. w.*, walls of "alveoli"; *bld.c.*, blood corpuscles; *co.*, cortex; *e.c.*, elongated cells; *n.*, nuclei; *me.*, medulla.

The arrangement of the inter-renal and the "paired suprarenals" of Elasmobranchs at once suggests the possibility of outstanding portions of both "cortical" and "medullary" constituents being found in the higher as well as in the lower

[1] Kohn, who repeated Stilling's observations, used the term "chromaffin," and called the bodies "paraganglia." More recently Poll has invented still another term, "phaeochrome." There seems to be no need for either of these,

vertebrates. And the same possibility was suspected long ago from other considerations.

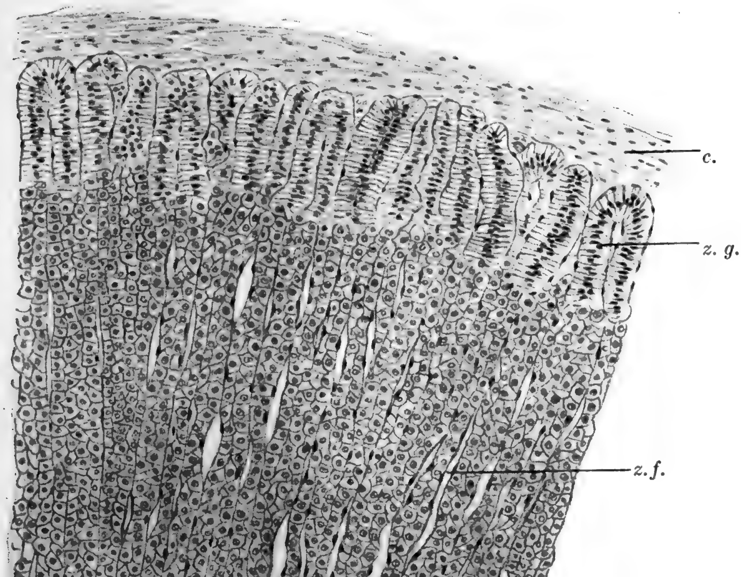


FIG. 29.—Section through portion of the adrenal body of a dog, showing the various zones of the cortex, and the medulla. (Drawn by Mrs. Thompson.)

c., capsule; *m.*, medulla; *z.f.*, zona fasciculata; *z.g.*, zona glomerulosa (zona arcuata); *z.r.*, zona reticularis.

The term "accessory adrenal" in mammals has been used in different senses. We must carefully distinguish between:

1. Bodies composed entirely of cortical substance—"accessory cortical bodies."[1]

2. Bodies made up exclusively of medullary substance—"chromaphil bodies."

3. True accessory adrenals composed of both cortex and medulla.

The *accessory cortical bodies* represent by far the larger number of structures which have passed under the name of "accessory adrenals." They are said to show the three zones characteristic of the cortex of the adrenal of mammals, but no chromaphil cells are present—there is no "medulla." The smallest of these bodies are microscopic; others may reach a diameter of a centimetre or more. They are found in the neighbourhood of the chief adrenal, sometimes embedded in other organs, in the retroperitoneal space, or in the genital region, as, for example, in the ligamentum latum, or in the space between testis and epididymis, where they are known as "Marchand's adrenals."

The Chromaphil Bodies.—These are found, or may be found, in any part of the body into which the sympathetic nervous system extends, and more particularly as groups of cells in connection with the abdominal sympathetic and its extensions. In connection with the abdominal sympathetic they were first noted and described by Leydig and called "Kernnester" by Mayer. The observations of both these authors applied to the Urodela.

But the recognition of the chromaphil cells and corpuscles in mammals and the characteristic reaction with chromium, by which they are now designated and homologized with the medulla of the adrenals, are due to Stilling. This author found in the abdominal sympathetic small bodies composed of cells having the same chromaphil reaction as those forming the medulla of the adrenal. He states that some are nearly a centimetre in length, while others are only just visible to the unaided eye. They are round, oval, or elongated in form, and their thickness is never more than a few millimetres. They have a tunica propria, small vessels and capillaries. Between the capillaries are cells which resemble in all respects those of

[1] The term "accessory inter-renal bodies" has been sometimes applied to them, but it seems best to avoid the term "inter-renal" except as applied to the Elasmobranchs.

the adrenal medulla. The resemblance between the chromaphil corpuscles of the sympathetic and the medulla of the adrenal is rendered all the greater by the occurrence in the latter of occasional nerve cells. Stilling found these corpuscles in the rabbit, the cat, and the dog, and especially in young animals. He gives details of a method for displaying them.

This extracapsular chromaphil material is still very imperfectly understood by many writers on the physiology and pathology of the adrenals. Thus Rolleston refers to Zuckerkandl's "parasomata"—the carotid body, the coccygeal, and "some cells in the pituitary." Now, the coccygeal body does not contain chromaphil cells, nor the pituitary, so far as I am aware. But the writer omits all reference to a very striking mass of chromaphil tissue (the paraganglion aorticum of Kohn)—the abdominal chromaphil body—which is present in the ordinary laboratory animals.[1] This important body can readily be displayed in the dog, for example, by removing the liver and alimentary tract from the abdomen, and placing a piece of absorbent cotton soaked in a solution of potassium bichromate (3 to 5 per cent.) over the retroperitoneal tissues for six to twelve hours. On removing the whole of the remaining tissues and washing in running water for a few hours, the chromaphil bodies are plainly visible, and still more plainly if the whole preparation be placed in glycerin. The "abdominal chromaphil body" is revealed by this method as a very dark brown wavy streak of irregular diameter, placed

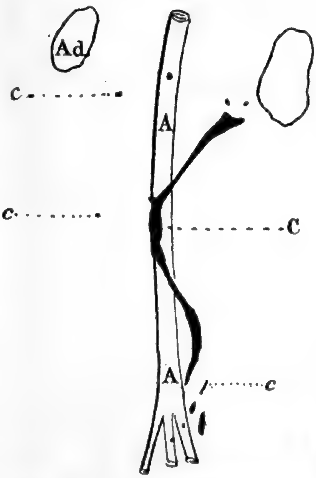


FIG. 30.—Abdominal chromaphil body of an adult dog.

Lettering common to Figs. 30, 31, and 32.—*A.*, aorta; *Ad.*, adrenal; *C.*, abdominal chromaphil body; *c.*, smaller chromaphil bodies.

[1] It seems possible that the "abdominal chromaphil body" of the dog may correspond to the "Nebenorgan" of Zuckerkandl. But the general shape and appearance of the two bodies are quite different, and Zuckerkandl's body was found only in very young subjects.

in front of the aorta and extending from the region of the adrenals in front to the bifurcation of the aorta behind. Other elongated, oval, or rounded patches or specks of chromaphil tissue are also visible in different regions.[1]

Figs. 30, 31 and 32 will give an idea of the arrangement of the abdominal chromaphil body and other smaller chromaphil corpuscles in the dog, the cat, and the rabbit respectively.

Numerous irregularly disposed smaller masses of chromaphil tissue are found in different regions more or less closely related to the principal chromaphil body [see Figs. 30, 31, and 32 (*c*)].

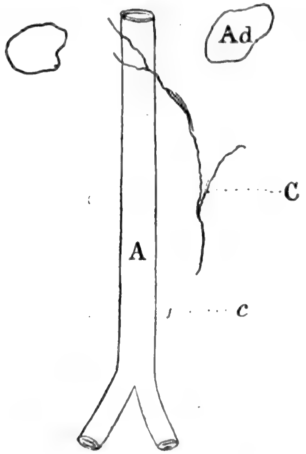


Fig. 31.—Chromaphil bodies of adult cat.
Lettering same as for Fig. 30.

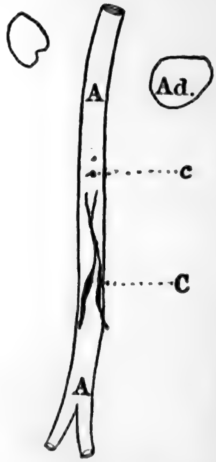


Fig. 32.—Abdominal chromaphil bodies of a rabbit.
Lettering same as for Fig. 30. The principal body is bifurcated anteriorly and posteriorly.

In the cat (Fig. 31) the chromaphil body tends to consist of long threads of tissue. These threads are stretched along the sympathetic, and the relationship to the nervous system is more obvious than either in the dog or the rabbit.

In the rabbit (Fig. 32) there is a distinct tendency for the principal chromaphil body to be paired, or it may be bifurcated anteriorly and posteriorly [Fig. 32 (*C*)]. The threads of

[1] I am indebted to the late Dr. Stilling and to Dr. Kohn for their kindness in giving me detailed instructions as to how to find these bodies, and to Dr. Kohn for some specimens which he generously sent me.

chromaphil tissue frequently run close up to, and may even be continuous with, the medullary substance of the adrenal.

In some animals—viz., monkey, pig, guinea-pig, rat, gopher, and squirrel—the present writer has been unable to discover any chromaphil bodies.

In regard to the microscopic structure of the chromaphil bodies, a detailed description is not necessary. It is, however, desirable to institute some comparisons between the histological

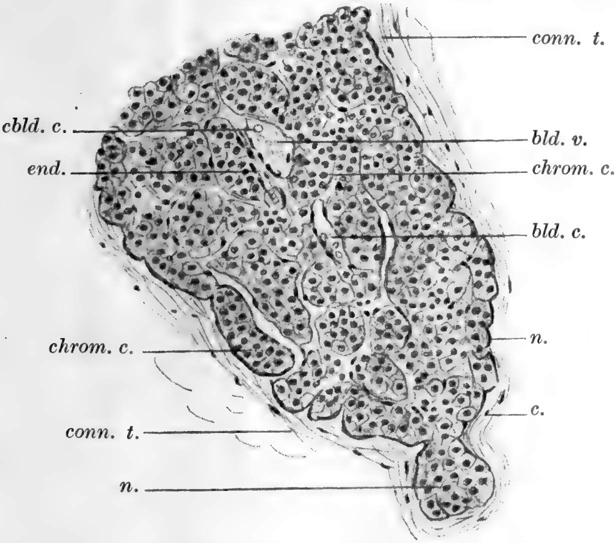


FIG. 33.—Transverse section through the abdominal chromaphil body of the dog. Fixed in corrosive sublimate and stained with hæmatoxylin. Section 10 μ in thickness. Leitz obj. 6. Drawing ocular.

Lettering common to Figs. 33, and 34, *bld. c.*, blood corpuscles; *bld. v.*, blood-vessels; *c.*, capsule; *chrom.c.*, chromaphil cells; *col.c.*, columnar cells of adrenal medulla; *conn. t.*, connective tissue; *end.*, endothelium of blood-vessels; *n.*, nuclei.

appearances of the adrenal chromaphil tissue and this substance as it occurs in other places, as, for example, in the sympathetic ganglia and in the abdominal chromaphil bodies. These comparisons refer to the structures in the dog.

A comparison of Fig. 33 with Fig. 34 will show that the general resemblance between extra-adrenal chromaphil tissue and adrenal medulla is very great. Both consist of columns of cells staining yellow or brown with bichromate of potash. The cell columns are, however, for the most part much thicker

in the adrenal than in the abdominal chromaphil bodies. The blood spaces are wider, and the whole aspect gives the impression that the adrenal medulla is more highly organized [see Fig. 34 (*bld. v.*, *col. c.*)].

Many of the cells of the adrenal medulla are spherical, as in the abdominal chromaphil body, and their dimensions are the same—viz., about 12 μ in diameter. The nuclei, also, are of the same order of magnitude in the two cases—viz., 5 μ or 6 μ. But in many regions, especially where the cell columns are

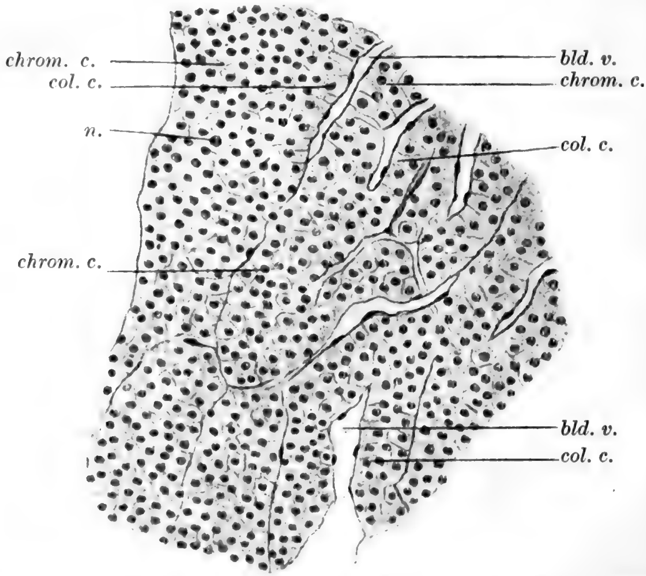


Fig. 34.—Section through the medulla of the adrenal of a dog, prepared as in case of previous figure. Same magnification. Lettering same as for Fig. 33.

separated by large venous sinuses, the cells are arranged in a definitely epithelial fashion round the bloodvessels [Fig. 34 (*col. c.*)]. In this case the cells are columnar in shape, and may reach a length of 26 μ, and the nuclei are placed at the end of the cell remote from the bloodvessel.

The protoplasm of the adrenal medulla is more distinctly granular than that of the abdominal chromaphil body, and is, moreover, more delicate in consistence, and therefore shows more shrinkage in fixation and tearing during the process of cutting sections. When the adrenal is fixed in bichromate

solutions, the section shows vacuoles as do those of the chromaphil body. These are absent in sublimate and Flemming preparations.

Thus it seems justifiable to regard the medulla of the adrenal body as composed of chromaphil cells of the same general character as those forming the chromaphil bodies. But the former have undergone specialization, and the structure of the substance has become elaborated into an organ with more definitely glandular form.

It is clear from all that has gone before that the extra-adrenal

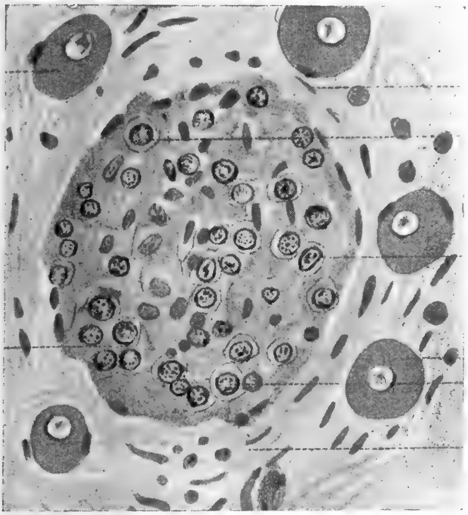


FIG. 35.—Section through a group of chromaphil cells in the inferior cervical ganglion of a dog.

chromaphil tissues contain a substance which gives the same macro- and micro-chemical reactions as adrenin. It has been shown by Biedl and Wiesel that the "parasomata" (Nebenkörper) discovered by Zuckerkandl in the human subject contain adrenin or some substance which has an identical effect upon the blood-pressure. The present writer has been able to prove that the abdominal chromaphil bodies of the dog contain the same or a similar substance. Fig. 36 shows the effect of injecting into the saphenous vein of a dog an extract from the chromaphil bodies of three dogs. It

will be seen that there is a very considerable and very characteristic rise of the blood-pressure.

The investigations of Stilling were confirmed and extended by Kohn and Kose, who laid stress on the fact that the chromaphil cells are common and typical elements of the mammalian sympathetic system. Kohn's view is that what is ordinarily called the "cortex" of the adrenal is in reality the only part which ought to be called adrenal at all, while the medulla is simply the "paraganglion suprarenale," a group of what he called "chromaffin" cells, which have become included in the adrenal. This matter will be referred to again later on.

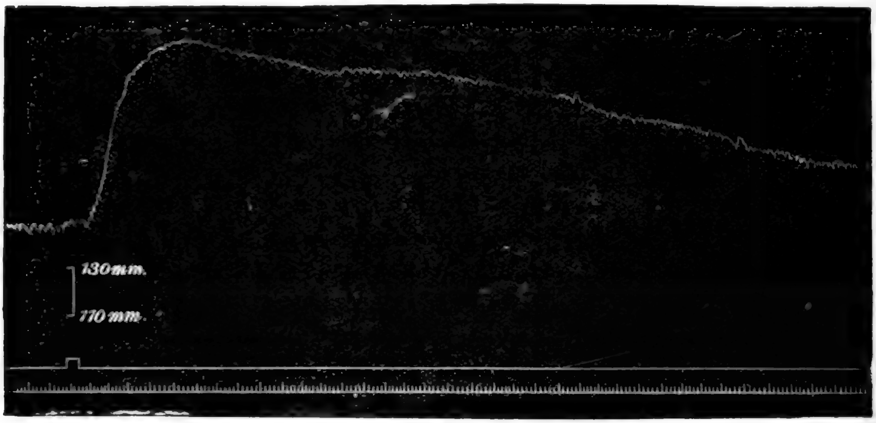


FIG. 36.—Dog, 8 kilogrammes. November 10, 1909. $CHCl_3$, morphine, atropine. Carotid blood-pressure. Time in seconds. At the point signalled an extract from the chromaphil bodies of three dogs was injected into the saphenous vein.

Zuckerkandl in 1901 found in the retroperitoneal space at the origin of the inferior mesenteric artery a pair of large chromaphil bodies, which he called "Nebenkörper des Sympathicus." These he found constantly in the embryo and in the new-born human subject, and, as we have seen, Biedl and Wiesel found that the bodies contained a pressor substance.

True accessory adrenals, containing both cortex and medulla, like the main gland, are said to occur in the neighbourhood of the abdominal sympathetic, and in the region of the body where the cortical elements first arise.

6. *Tabular Statement of Chief Facts in Comparative Anatomy of the Adrenals*

The table [1] on page 126, modified from Poll, will render clear the chief facts in the comparative anatomy of the adrenal system.

In concluding this section we would call special attention to Figs. 37 and 38, which give in a diagrammatic form a comparison of the adrenal representatives in Elasmobranch fishes and in mammals respectively.

C. Development of the Adrenals

Balfour expressed the view that "in Elasmobranch fishes we thus have (1) a series of paired bodies, derived from the sympathetic ganglia, and (2) an unpaired body of mesoblastic origin. In the Amniota these bodies unite to form the compound suprarenal bodies, the two constituents of which remain, however, distinct in their development. The mesoblastic constituent appears to form the cortical part of the adult suprarenal body, and the nervous constituent the medullary part." This hypothesis has been fully supported, and the observations leading to it have been completely confirmed by all subsequent work upon the embryology of the adrenals. In the various classes of vertebrates there have been numerous observations, all of them clearly pointing out the totally distinct

[1] In the table, the term "cortical system" has been substituted for "inter-renal system" employed by Poll. Each of the alternative terms has a certain and a similar disadvantage, inasmuch as it refers to an anatomical arrangement which is not universal throughout vertebrates, but confined to a single group—the term "inter-renal" being only applicable to Elasmobranchs, the term "cortical" being only applicable to mammals. But it seems on the whole preferable to use the word "cortical," because it refers to the arrangement in mammals which will long continue to serve as the standard of comparison in the organology of the adrenal system.

Further, as announced previously, it is proposed to use the term "chromaphil" instead of "chromaffin" or "phæochrome." There is no doubt that in some respects "phæochrome" is the best word, but "chromaphil" is only a slight modification of the original "chromophil" employed by Stilling, and was suggested to me by Sir Edward Sharpey Schäfer.

It is a pity that we cannot for the "cortical" cells use some name which would describe their staining reaction, or the chemical nature of their contents. But the literature of the comparative anatomy of the adrenals is already overburdened with a complicated and abtruse nomenclature, so perhaps it is best to be content with the term "cortex."

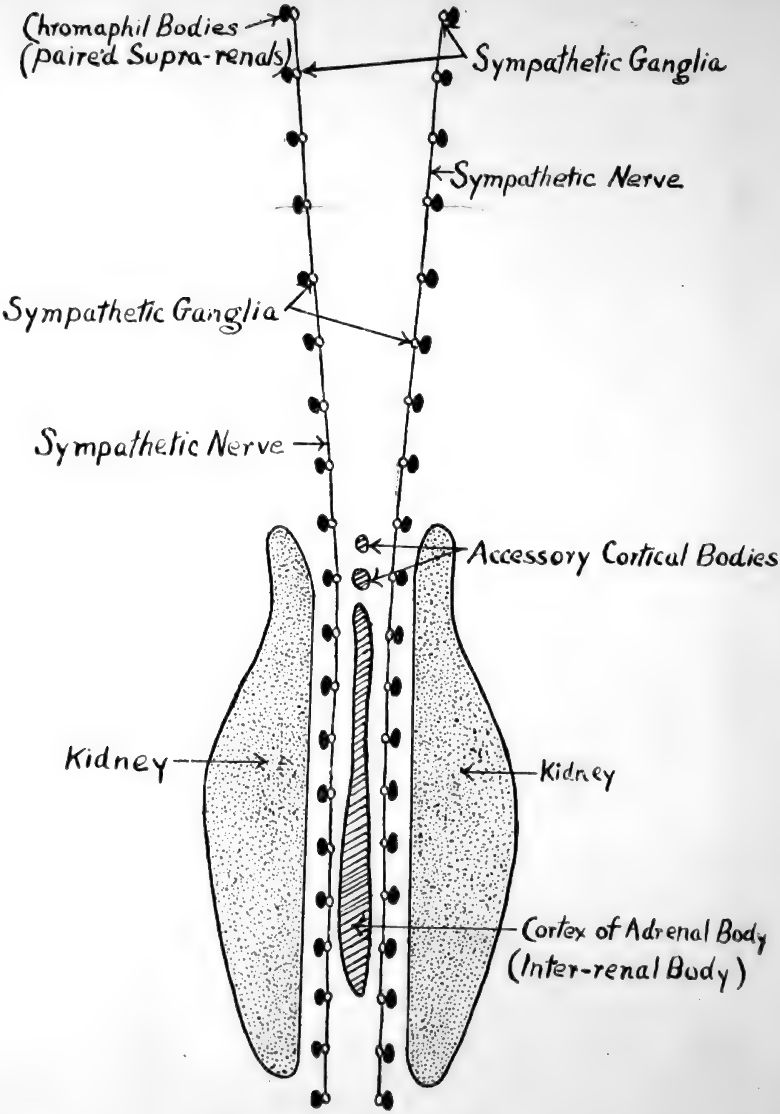


FIG. 37.—Diagram of the adrenal representatives in elasmobranch fishes showing the cortical gland (inter-renal body) and the medullary glands (chromaphil bodies, "paired suprarenals") in relation to the sympathetic and the kidneys.

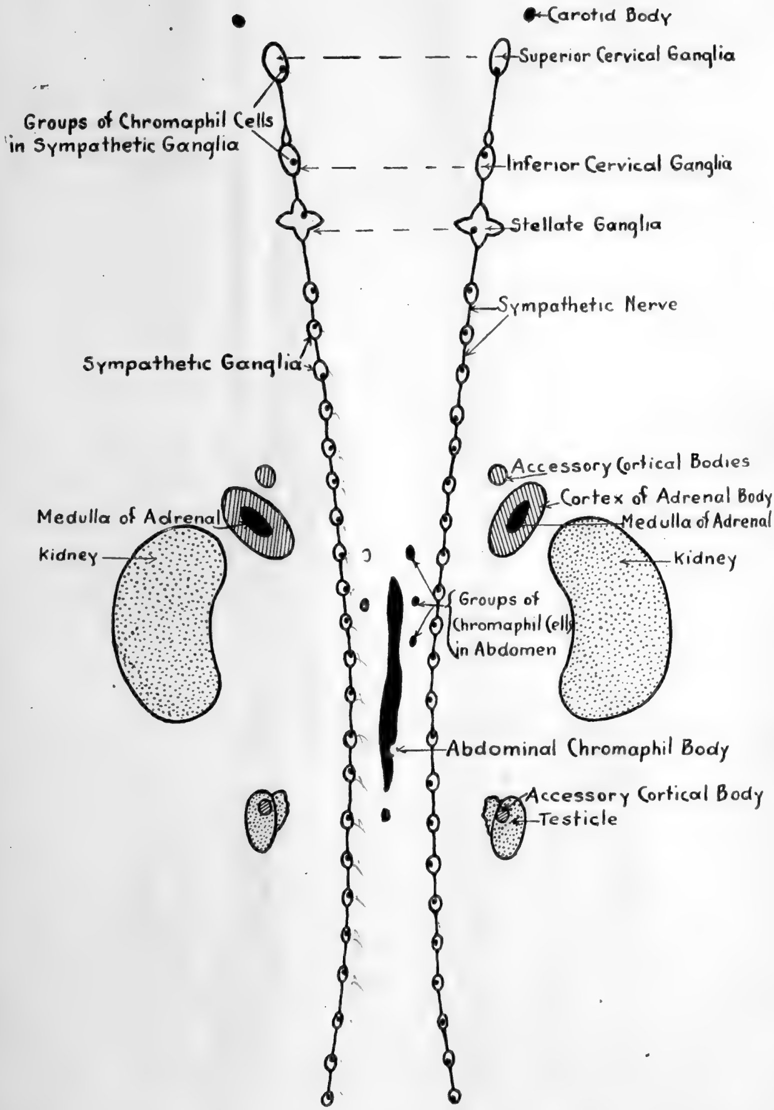


FIG. 38.—Diagram of the adrenal constituents and outstanding "cortical" and "medullary" (chromaphil) bodies in the mammal, showing the adrenal bodies, the chromaphil cells of the sympathetic, the abdominal chromaphil body ("accessory medullary") and accessory cortical adrenals in relation to the sympathetic and the kidneys.

VERTEBRATA.

CORTICAL SYSTEM.

Cortical Bodies.

Cyclostomata and Pisces.

Petromyzonta : Cortical bodies.
Selachii : Inter-renal bodies.
Teleostei : Cortical bodies.
1. Caudal inter-renal bodies (corpuscles of Stannius).
2. Cranial cortical bodies (Giacomini).

Ganoidei : Cortical bodies scattered through substance of kidney.

Cortical Bodies.

Amphibia and Amniota.

So-called "accessory adrenal bodies."
"Marchand's adrenal bodies" in mammals.
"Accessory cortical adrenal bodies."

Cortex Medulla
$\underbrace{\qquad\qquad}$
of the
Adrenal Body.

CHROMAPHIL SYSTEM.

Chromaphil Bodies.

Petromyzonta : Chromaphil corpuscles.
Selachii : Chromaphil corpuscles ("paired suprarenals").
Teleostei, *Ganoidei* : Chromaphil corpuscles (Giacomini).

Chromaphil Bodies.

Amphibia : "Cell nests."
Reptilia : Wiesel's corpuscles.
Mammalia : Zuckerkandl's "parasomata" (Nebenorgane).
Abdominal chromaphil body.
Chromaphil part of carotid body.
Amniota : Chromaphil cells and corpuscles of sympathetic nerves and ganglia.

origin and nature of the cortex and the medulla. It will only be possible to refer to some of the more important papers.

Mitsukuri worked out the development of the adrenal body in the rabbit and in the cat. He concluded that the cortical substance arises from the mesoblast, while the medullary substance is derived from the peripheral part of the sympathetic nervous system, and is at first placed outside of the cortical substance, becoming transported into the middle of the adrenal body in the course of development. That the cortex is derived from the mesoderm and the medulla from the same blastema as the sympathetic ganglia is now almost universally conceded.

The cortical substance is developed from the cœlomic epithelium in a region known as the "adrenal zone." The extent of this zone varies in different vertebrates. In mammals the origin of the cortex appears to be from the cœlomic epithelium on either side of the root of the mesentery or a little caudalwards from the cranial end of the primitive kidney, appearing first as a series of buds which subsequently grow together.

In regard to the development of the medulla of the adrenal body, it has been ascertained that certain cells derived (along with the sympathetic generally) from the neural ectoderm, do not develop into nerve cells, but into chromaphil cells. In the anamnia below the amphibia, these do not enter into any relations with the cortical elements, but remain as chromaphil bodies or corpuscles. In Amphibia and in the Amniota some of these chromaphil cells grow into the cortical gland and form its medulla. Ultimately these acquire the chromaphil substance. It is stated that in man this is not actually found in them until some little time after birth, but it occurs in the embryo of the ox and the sheep long before birth.[1]

D. Addison's Disease and the Pathology of the Adrenal Bodies

1. *Introductory and Historical*

The medical practitioner directs his inquiries towards experimental physiology and pathology in order to ascertain how far

[1] Bruni in 1912 described the development of the chromaphil tissues in *Rana esculenta*. The chief point of importance in this paper is the observation that the chromaphil substance is not derived from the sympathetic, but only

modern research will enable him to understand the clinical phenomena of Addison's disease, and to treat his patients in a scientific spirit. On the other hand, the physiologist is eager to acquire whatever information can be derived from the realms of clinical pathology and pathological anatomy, as to the functions of the adrenal bodies. The fuller and more accurate is our knowledge of diseased conditions of the organs, the sounder will be our progress in both these conditions. Pathology has taught us something of the adrenals, and physiology has contributed certain facts of primary importance. It must, however, be admitted that it is not possible at the present time to combine the knowledge derived from these two sources in such a way as to give an intelligent explanation of the functions of the adrenal bodies, and at the same time to offer a satisfactory explanation of the symptoms of Addison's disease.

Addison's disease is characterized by the cardinal symptoms of extreme muscular weakness, nausea and vomiting, and an exaggeration of the normal pigmentation of the skin.

Addison attempted to elucidate the nature of a malady which he had styled "idiopathic anæmia," from an inability to associate it with any exact pathological condition. He was thus led to the discovery of the diseased state of the adrenal bodies, and the association between this diseased state and the train of symptoms which bears his name. The observations were confirmed but not much extended by Wilks, Trousseau, and Greenhow. It was Trousseau who first used the term "Addison's disease." It must be admitted that comparatively little has been added to our knowledge of the clinical aspect of the disease since it was first described.

Addison considered that any lesion of the adrenal bodies which would interfere sufficiently with their function would give rise to the disease. Wilks and Greenhow were, however, of a different opinion—viz., that the true morbus Addisonii has essential peculiarities of its own, that no other disease or degeneration of the adrenal bodies is capable of producing the same associated train of symptoms. The modern view is entirely in accordance with that first expressed by Addison, that the symptoms are due to an interruption of, or a deficiency in, the functional activity of the adrenal bodies.

secondarily comes into contact with this system. The chromaphil cells appear first in close relation with the walls of certain bloodvessels.

2. *Symptoms*

1. *Pigmentation.*—The pigmentation is very variable both as to its period of onset and as to its intensity. Usually it first occurs at a later period of the disease than the general symptoms, such as the muscular prostration. It sometimes occurs only shortly before death, and in some cases it never occurs at all. Occasionally, however, the pigmentation has been stated to precede the general symptoms.

As for the degree or intensity of pigmentation, it may vary from the dark hue of the negro to a faint sunburn brown. It is very interesting to note that the pigmentation is an exaggeration of the normal, and occurs most markedly in those parts which are normally pigmented, such as the dorsal surface of the forearm, the axillary folds, the areola around the nipples, the genitals, and the groins. The pigmented regions have no sharp margins. Friction or pressure induces especially the increased pigmentation; thus we find dark patches or streaks brought about by corset, belt, garters, braces, or collar-stud.

Pigmentation is usually first noticed on the face, neck, and backs of the hands and fingers, especially over the joints. The lips may sometimes become pigmented and the tongue occasionally presents stains near the free border. There are also to be seen in some cases small, well-defined specks, like small moles, but occasionally of inky blackness. Pigmentation of the peritoneum and pia mater has been recorded. The hair may become darker, but the skin of the hairy scalp and other regions covered by hair does not appreciably change in colour. The linea alba may become a dark line. Rolleston says that the palms of the hands and the soles of the feet are very rarely pigmented, but he has twice seen pigmentation of the palms with intensification along the various lines.

Microscopically the pigment is found in the cells of the stratum Malpighii, and the dermis shows a few pigmented cells—"carrier cells"—which, it is thought, convey the pigment from the bloodvessels of the dermis to the stratum Malpighii.

The pigment is iron-free. In some few cases a combination of Addison's disease with hæmochromatosis has been reported. Pigmentation occurs in about 75 per cent. of all cases.

2. *Asthenia.*—Many authors regard the asthenia or muscular weakness as the most constant and the most significant of

all the symptoms of Addison's disease. The patient suffers from an almost complete indisposition for any exertion. He is very easily tired, and is never able to get properly rested. There is no corresponding emaciation or neuritis.

Asthenia is almost always the earliest sign of the disease. Long before one notices any change in the skin the patient complains of extreme lassitude. He can perhaps make a short series of movements with some energy, but he is almost immediately fatigued. Langlois lays great stress on this feature, and recommends the use of Mosso's ergograph as an instrument of diagnosis. He states that what characterizes the patient with Addison's disease is not so much the loss of ability to perform a single muscular feat, as a more or less complete disappearance of resistance to fatigue. If one submits under the same conditions a patient with Addison's disease, and another patient in a comparable condition (both, for example, tubercular to the same extent), to the ergographic test, we find that the fatigue curve is quite different in the two cases. We find that the simple tubercular patient can carry out a sustained labour (lift a weight of 1 kilogramme every two seconds) for a certain time; but the patient with Addison's disease, who at first will lift the same weight to the same height, soon becomes exhausted; his curve shows a rapid fall.

3. *Other Symptoms.*—The majority of authors report that in Addison's disease the blood-pressure is remarkably low. The heart is feeble in action; there is a small, soft, almost imperceptible pulse. From the evidence before us we are not justified in stating that a low blood-pressure is constant.

The temperature is usually subnormal.

In regard to the condition of the blood, some authors state that anæmia is not characteristic, though the patients present an anæmic appearance. Others affirm that the blood always shows changes, in the directions of diminution in number of the red corpuscles and lowered hæmoglobin content. The number of leucocytes is in most cases normal. It has been stated also that the eosinophilous cells and the large mononuclear cells are increased in number. Status lymphaticus is not rare, and hyperplasia of the thymus has been observed. It is stated that there is no very marked emaciation in the majority of cases.

Vomiting is very common, and there is frequently hiccup

and sometimes diarrhœa. But there may be constipation from loss of muscular tone.

Sometimes there is an alternation of constipation and diarrhœa, which latter frequently occurs without obvious cause. Towards the end there may be pain with retraction of the abdomen, and small pulse, the condition strongly suggesting peritonitis.

Various symptoms referable to the nervous system have been described. Some of these, such as twitchings and convulsions, point to irritation of the nervous system, but the most characteristic, such as a diminished or absent knee-jerk, are indications of depressed activity of the nervous system. Headaches and faintness are not uncommon.

Insomnia, loss of memory, noises in the ears, vertigo, pains in the trunk and limbs, and mental symptoms with hypochondria are also mentioned.

The "white line" of Sergent has been recommended as a test for adrenal insufficiency. The method employed is to outline a square about the umbilicus with a blunt object by quite superficial stroking without using pressure or scratching. The patient should be kept still, and after half a minute, a pale line or band begins to appear which gradually becomes more distinct and white. It attains its maximum clearness in about one minute, persists for two or three minutes, and gradually disappears. The theoretical explanation given by Sergent is not satisfactory. The normal response to light stroking appears to be a brief vaso-dilation followed by a vaso-constriction. The failure of this normal reaction is stated to be a sign of adrenal deficiency.

3. *Etiology and Onset*

The disease is rare. It is doubtful whether one sex is affected more than the other ; it occurs about the thirtieth year on the average. The adrenal bodies may become infected in tubercular patients from the mesenteric glands or from disease of the vertebræ. But the adrenal bodies themselves seem to be susceptible to primary tuberculosis, and are often the only seat of tubercular infection in the body.

Strains and injuries to the back or blows on the abdomen have sometimes been alleged to be the cause of the mischief. In these cases the trauma might render the gland more liable

to infection. Traumatic hæmorrhage into the substance of the gland has been stated to be the starting-point of the lesion in some cases.

The onset is nearly always insidious and gradual. Gastric trouble is perhaps one of the commonest causes of the patient's seeking advice. Very rarely the disease seems to come on suddenly after a shock or some cause of worry. It may be congenital.

4. *Metabolism in Addison's Disease*

Owing to the rarity of Addison's disease, little is known as to the general (total) metabolism. Nor have we any *a priori* grounds for assuming that this would be either increased or diminished.

According to a brief account given recently by Richter, the protein metabolism is not appreciably affected. Senator and Pickardt observed either nitrogenous equilibrium or, with abundant food, nitrogenous gain. On administration of adrenal substance to the patient there was no increase of protein destruction.

There is an increase in the phosphoric acid elimination. Richter suggests that this has to do with increased destruction of bone substance, though Senator found the calcium elimination not raised.

Nothing certain is known of any change in carbohydrate metabolism. We might expect, since adrenin pharmacodynamically induces glycosuria, that in Addison's disease, where there is presumably a deficiency of this substance, we should find a lowering of the sugar content of the blood. In experiments upon animals after extirpation of the adrenal bodies, this is actually found to be the case, but the clinical evidence in the case of the human subject is meagre and conflicting, although Bernstein and Falta believe that hypoglycæmia is a sign of some diagnostic value.

There seems to be actually a diminution of the urinary pigments.

5. *Morbid Anatomy*

In Addison's original paper eleven cases are recorded. In five of these there was caseous tubercle in both adrenal glands, and in one case tubercle was only present in one gland. One

case seems to have been an example of cirrhosis and atrophy. In three cases there were secondary carcinomatous growths in the adrenals, bilateral in one case, unilateral in the other two. In one additional case there was a secondary nodule of carcinoma blocking the right suprarenal vein, and associated with hæmorrhage into the corresponding gland, but there were no growths in either.

Bittorf states that in all cases there is disease of both adrenals. This may be (1) simple atrophy, or (2) inflammatory atrophy (chronic interstitial inflammation) with shrinkage and destruction of the parenchyma, resembling cirrhosis. According to this author, there is no special part of the gland which is of prime importance to life. He considers that the adrenal bodies are single organs, clearly essential to life, interference with which causes a definite train of symptoms. From the tone of this writer it would appear that he does not clearly recognize the essential and fundamental difference between the cortex and the medulla, nor does he appear to appreciate fully the significance of the fact that even if cortex and medulla do really constitute one physiological structure, there are outstanding masses of both constituents in different regions of the body, concerning which it would be out of the question to make a similar hypothesis. There may yet be discovered some reason for looking at the adrenal gland (cortex and medulla taken together) as a functional whole, but Bittorf appears to have come to this conclusion simply because the experimental evidence as to the respective importance to life of cortex and medulla is conflicting, and because pathologists have never yet been able to determine any difference in those cases where chiefly cortex or chiefly medulla have been involved.

Winkler gives an account of twenty-four cases of adrenal tumours. There were thirteen primary growths (ten epitheliomata and three sarcomata), and eleven secondary cases. In only two cases was there any bronzing of the skin. From a careful study of these cases the author is quite unable to decide whether Addison's disease is due to an affection of the cortex or of the chromaphil tissue and the sympathetic, or is to be attributed to a lesion of both together.

In cases of Addison's disease a fibro-caseous condition of tubercular origin is by far the commonest condition found. In addition, simple atrophy, chronic inflammation, syphilis,

malignant disease, and extravasation of blood have been recorded. The solar plexus and semilunar ganglia as well as the ganglia and nerves in the adrenals are often the seats of alterations. They may be atrophied from the pressure of tumours, affected by tuberculosis by extension or as part of a widespread invasion, or they may be involved in inflammatory processes (Dock).

Hyperplasia of lymphoid tissues has been described.

Wiesel has described in six cases of Addison's disease severe degenerative changes and destruction of the chromaphil cells not only in the adrenal medulla, but also in the sympathetic. He reports, further, that in a case of tuberculosis of both adrenal bodies, where there had been no symptoms of Addison's disease, not only was there no destruction, but there was a hyperplasia of the chromaphil tissues. Wiesel then, regards Addison's disease as due to a primary lesion of the chromaphil tissues. It is clear that such cases were easily overlooked by the earlier pathologists, and may account for some of the reports of Addison's disease without lesion of the adrenals.

6. *Pathogeny.*

The theories as to the pathogeny of Addison's disease may be divided into two groups: (1) Nervous, (2) chemical or glandular.

If we except Addison's original view (which he somewhat modified later on) and the theory that the adrenals are of no importance in the economy, most of the early theories were nervous. The view of Wilks and Greenhow was that the lesion is special and primary in the adrenals, while the symptoms of the disease are due to the secondary effects on the adjacent sympathetic, the solar plexus, and the semilunar ganglia. But in many cases of typical Addison's disease no changes in nervous structures could be found, and on the other hand there are numerous examples of irritation of sympathetic ganglia where no symptoms of Addison's disease have occurred. It may be, however, that the vomiting is of a nervous nature, and due to some effect upon the autonomic nervous system.

The chemical or glandular theory is the one now generally accepted. It is usually subdivided into two: (1) The auto-intoxication theory; and (2) the theory of internal secretion.

According to the latter view, the pathology of Addison's disease is to be explained on the basis of *adrenal inadequacy—i.e.*, an interference with the normal internal secretion of the gland. According to the former, the symptoms of Addison's disease are due to the accumulation of poisonous products (*e.g.*, of muscular activity), to remove which it is the duty of the adrenal body. It seems clear that the gland does not effect this removal after the manner of an excretory organ, but there is nothing to prevent our supporting the hypothesis that the secretion of the gland has for its function, or one of its functions, the neutralization of some of the poisonous products of metabolism.

If we admit that one of the functions of the secretion of the gland is to maintain the tone of muscular structures generally, then we have at once an explanation of the extraordinary muscular prostration in Addison's disease. But the effects of adrenin, the secretion of the chromaphil medulla, are practically confined to the muscular structures under the control of the sympathetic nervous system. It may be that the muscular weakness is to be explained on the hypothesis that the adrenals in some way neutralize the poisonous products of muscular activity.

But how are we to explain the pigmentation, the bronzing of the skin, which is, after all, the most striking of all the symptoms of Addison's disease? Is this symptom related to the colour reactions given by the chromaphil cells of the medulla, and extracts made from them, or is it related to a destruction of red blood-corpuscles which is stated to occur in the central portion of the cortex, or is it due to deficiency in some other function of cortex or medulla?

It seems difficult or impossible to induce pigmentation by experiments upon animals (see, however, pp. 141 and 142).

The pigment is disposed for the most part in places which are exposed to thermal, chemical, and luminous stimuli. From a teleological standpoint the pigmentation might be regarded as a protective arrangement against luminous stimuli. According to Bab (in discussing melano-sarcoma of the ovary), pigment raises the power of resistance of tissues and organs, and is therefore found in the *locus minoris resistentiæ.* In this view the pigment is a general means of protection against injury. Eiselt comments that this can scarcely hold as a general theory,

for pigment becomes developed in large amount in ganglion cells only during the process of degeneration.[1] Wieting and Hamdi, discussing melanin-pigmentation, regard the formation of pigment as a protective arrangement—*e.g.*, it is laid down in the skin to protect the underlying structures. Solger looks upon the skin pigment as a protective against ultra-violet light.

The pigments of the body (respiratory, biliary, urinary, melanins, lipochromes, etc.) may be divided into—(1) iron-containing pigments; and (2) fat-containing pigments. The second group includes the degeneration pigments, the lipochromes, and the melanins. The pigment in Addison's disease appears to belong to the melanins.

There are various theories as to the mode of formation of the pigment. It has been suggested that it arises as a result of over-activity of the cells of the stratum Malpighii, due to increased nervous stimulation, the result of mechanical irritation of the nerves round the adrenals. Eiselt believes that in consequence of the failure of the antitoxic adrenal function (of the cortex) the accumulated products act autolytically upon the protein. Then, by the action of tyrosinase upon the aromatic molecular complexes thus formed, there arises an accumulation of melanin.

A modification of this theory, but involving the hypothesis that the *medulla* is concerned in the pigmentation, based upon the work of v. Fürth and Halle has been put forward by Adami. The melanin appears to be formed by the action of oxidases upon tyrosin and other aromatic products of protein decomposition. It seems possible that adrenin is manufactured in a similar kind of way, so that when the adrenal bodies are diseased the tyrosin and allied bodies accumulate in the tissues, and the greater darkening of the superficial parts most exposed to light and air gains its explanation from the more active oxidation of those aromatic bodies in these regions.

Pathologists have never until quite recently given due consideration to the essential difference between the cortex and medulla of the adrenals. We have seen that these represent two separate and distinct kinds of tissue, which only come into relation with each other in the higher vertebrates, and

[1] There seems no reason why this pigmentation in degenerating nerve cells should not be an example of a protective effort (albeit ineffective) on the part of the cell.

consist of " cortex " and " medulla " only in mammals. It is possible that pathology may yet throw some light on the question of the function of the cortex and the question as to a possible physiological relationship between the two constituents of the gland.

We must remember that there are undoubted cases of Addison's disease in which both adrenal bodies are found to be healthy, and that there are other cases in which clinically no signs of the disease are present, but which at the autopsy show destruction of both glands. These facts may possibly find their explanation in the distribution of cortical and chromaphil substance outside the adrenal bodies. On the other hand, it seems not out of the question that we may have to resuscitate a long-buried hypothesis that the disease may sometimes be due to affection of the sympathetic nerves or ganglia. To bear in mind such a possibility is not so unjustifiable when we consider to how small an extent we are able to explain any of the symptoms of Addison's disease by anything we have learnt about the functions of the adrenal bodies.

In the meantime pathologists would do well to investigate, in all cases of probable adrenal disease, not only the adrenals themselves, but the rest of the cortical and chromaphil tissues in the body.

7. *Course and Event of the Disease—Diagnosis, Prognosis, and Treatment*

The course of the disease is usually progressive, but the mode of progress is paroxysmal [Greenhow]. All the symptoms are progressive, but not steadily so. The course of the disease on the whole is slow and chronic ; but it is subject to alternate exacerbations and remissions. During the remissions strength is to some extent recovered, but after each exacerbation the patient finds himself upon a lower level than during the previous remission.

In cases where destruction of the glands is produced by hæmorrhages or thromboses death may occur very rapidly with acute nervous and intestinal symptoms. In these pigmentation is absent.

In young subjects the disease may run a latent course—that is, the constitutional symptoms first appear suddenly in a fully developed form producing death in a few days.

The diagnosis must depend largely on the extraordinary lack of resistance to fatigue, upon the other constitutional symptoms, and upon the bronzing of the skin. Where this last is absent the diagnosis must be difficult and uncertain.

The prognosis is grave, but the patient may live a considerable time, and care should be exercised in foretelling to what extent life may be prolonged. At least one case is reported where the symptoms of Addison's disease have completely disappeared (Treckin).

The treatment will be dealt with under the therapeutic applications of adrenal substance (p. 204).

8. *Other Conditions involving Adrenal Insufficiency*

Defective development of the adrenals is not infrequently associated with imperfect growth of the brain, particularly in cases of anencephaly and hemicephaly.

Total deficiency of the adrenal medulla has been reported. Wiesel records a series of cases of what he calls "hypoplasia of the chromaffin system."

Lavenson, Sergent, and Cooke have described cases of acute adrenal insufficiency, which may occur with symptoms resembling an acute poisoning. These are apt to occur in diphtheria, scarlet fever, typhoid fever, erysipelas, and chloroform poisoning. Sergent connects certain conditions which may supervene in typhoid fever with the syndrome of adrenal insufficiency.

French writers frequently refer to a condition due to adrenal insufficiency, in which muscular weakness or lack of tone and a low blood-pressure, along with digestive and nervous troubles are striking symptoms. They have even attributed the symptoms of "shell-shock" to adrenal insufficiency.

9. *Excessive Adrenal Function*

The fact that excessive production and pouring into the circulation of the thyroid secretion appears to lead to a very definite train of symptoms, has naturally suggested the question whether an analogous condition of excessive production of the adrenal secretion may be a factor of consideration in the production of disease.

The most striking effect of the adrenal secretion is a rise of blood-pressure. As pointed out by Adami, hyperpiesis, or

pronounced and continued rise of blood-pressure, is not an uncommon condition. Roger and Gouget report hypertrophy of the adrenals in a case of experimental arterio-sclerosis induced by lead intoxication, while several authors have noted a relation between arterio-sclerosis and hypertrophy of the adrenal medulla.

Three theories have been put forward to account for the hyperplasia of the adrenal bodies in arterio-sclerosis: (1) The hyperplasia is not the cause of the hypertension at all, but an "antitoxic hyperplasia" due to the effects of the accumulated products of metabolism which possibly also produce the hypertension; (2) the hyperplasia is the cause of the hypertension, but is secondary to a renal lesion; (3) the hyperplasia is the cause of the hypertension, and is primary and independent of the kidney mischief.

It is yet too early to state which of these is the correct view. The French writers insist that the adrenal hyperplasia is almost constantly associated with chronic interstitial nephritis. According to Pearce, it may equally be associated with chronic parenchymatous nephritis.

On the other hand, Mott states that in his experience in advanced arterio-sclerosis the adrenal medulla is more often atrophied than hypertrophied.

Several writers have assumed a functional increase of the chromaphil tissue in certain forms of diabetes mellitus, but the matter cannot be regarded as definitely settled. The same applies to the association of interstitial nephritis and hyperfunction of the chromaphil tissue.

10. *Adrenal Tumours*

Tumours of the adrenal body are perhaps most usually of interest as bearing upon hyperfunction of the organ. But since it is conceivable that in some cases the growths may determine a reduction in activity, it is better to treat of them in a separate section.

A. *Tumours of the Adrenal Medulla* (*Chromaphil Tissue*).—A few cases of medullary glioma have been described. Adenomata of the chromaphil tissue, or "paragangliomata" are also mentioned. The symptoms noted were arterio-sclerosis, and cardiac hypertrophy as well as disturbances of nutrition, and other signs of a more general character.

Malignant medullary hypernephromata also occur, and, although the chief interest of these cases depends on the distribution of the secondary growths, yet it will be advisable to give a short account of their most striking features. The syndrome associated with these growths was first described by Hutchison. Most of the cases occur in children two or three years old, and in many the earliest characteristic sign is a hæmorrhagic streak upon one or both upper eyelids. This is followed by exophthalmos and optic neuritis. The disease is always fatal, usually within six months. The primary tumour is believed to arise from the chromaphil tissue of the medulla of the gland, and consists of round or oval cells with large nuclei and a granular protoplasm. It is doubtful whether it is a sarcoma or a carcinoma.

B. *Tumours of the Adrenal Cortex.*—These may be divided into two groups. In the first are included the sarcomata, carcinomata, endotheliomata, and cysts. These for the most part only give rise to general results such as may be expected from benign or malignant tumours. In the second group are included the adenomata and hypernephromata. The clinical importance of these will be discussed later in connection with the relations of the adrenal cortex to the genital functions (p. 241).

E. Extirpation Experiments in Mammals

The earliest extirpations of the adrenals were performed by Brown-Séquard in 1856. He employed for extirpation of both glands forty-four rabbits, nine guinea-pigs, two rats, and several dogs and cats. All these animals died in nine to thirty-seven hours after the operation. For the unilateral operation this experimenter used sixteen rabbits, five guinea-pigs, two cats, and two dogs. All these died in twenty-three to thirty-four hours. Later he reported that two dogs survived removal of one gland for eight days. As a rule young animals survived the operation longer than adults. Brown-Séquard came to the conclusion that the death after adrenal extirpation was not due to adventitious lesions connected with the operation, but to a cessation of the function of the glands. He noted marked muscular weakness, but not vomiting or pigmentation, and he supposed that the absence of these two last symptoms is due to the rapidity with which a fatal result supervenes.

These views of Brown-Séquard were vigorously combated by many workers. Gratiolet performed several series of operations upon guinea-pigs, and came to the conclusion that extirpation of the right adrenal was just as serious as removal of both. This was soon disproved by Brown-Séquard, who succeeded in keeping three guinea-pigs out of seven alive for three weeks after right-sided extirpation.

Philipeaux succeeded in keeping white mice and also a certain number of rabbits alive after bilateral extirpation. He concluded that removal of the adrenals does not necessarily lead to death, and that where death ensues this is due to the operative proceedings or some circumstance connected with them, such as peritonitis, and that some animals can survive complete extirpation without showing any symptoms—that, in fact, the adrenals are no more essential to life than is the spleen. This view he firmly maintained, although three of his operated animals died in nine, twenty-three, and thirty-four days.

In order to test the matter further, Brown-Séquard performed a further series of experiments upon rabbits, and felt justified in affirming that the adrenals are more essential to life than are the kidneys, and thought that the survival of occasional animals is due to a vicarious assumption of the adrenal function by the thymus or the thyroid.

Harley employed among other animals the white rat, and found that this animal may indefinitely survive entire removal of the adrenals. From this Harley, as well as Philipeaux and Gratiolet, ascribed the fatal results in other animals to injury to adjacent nerves and bloodvessels.

The observations of Nothnagel deserve special mention. This observer, from clinical observations, thought that a chronic inflammation of the adrenals would be more likely to induce symptoms resembling those of Addison's disease than removal of the glands. Accordingly he resorted to the method of crushing the bodies. He operated upon 153 rabbits, and found that if the operation were performed upon the two sides with an interval of three or four weeks between, then the animals survived and showed no serious symptoms. Among the 153 bilaterally operated rabbits, Nothnagel observed in three cases pigment spots on the mucous membrane of the mouth. These were noticeable one, three, and five months after the second operation. The author did not, however,

attach any particular importance to them. He thought, indeed, that the disease of the adrenal glands had no immediate relation to pigmentation.

The statement that removal of both adrenal bodies does not necessarily lead to death was denied by Tizzoni. This author came to the conclusion that in rabbits the destruction of one or both of the adrenals results in death if sufficient time be allowed to elapse. He obtained similar results with dogs.

The opinion that unilateral extirpation could lead to death was strenuously opposed by Stilling, who found that young rabbits from which one adrenal had been removed could develop quite normally, and live more than a year without showing any untoward symptoms. In thirty cases investigated Tizzoni found pigmentary changes in thirteen. These came on at the earliest two months after the operation, and occurred exclusively in the mucous membrane of the nose and mouth. They were of the same character as those found in Addison's disease. Stilling was unable to confirm these results. Tizzoni considered that death, which might occur after removal of one capsule, was due to lesions of the nervous system.

Abelous and Langlois employed various means for experimental lesions upon the adrenals, such as ligature, crushing, and cauterization, but most frequently the last method was used. They report that after complete destruction of one gland some animals suffered a loss of weight and a small proportion died. After complete destruction of both adrenals most of the animals soon died. The duration of life could be increased by performing the operation at two sittings with an interval of several days between them. After destruction of a fifth part of each gland, with an interval of one or two days between the two operations, the animals could be kept alive, but there was considerable emaciation. If an interval of eight to fifteen days were allowed to elapse between the two operations, then the animals lived without symptoms. If the half of each organ were cauterized away, the animals rapidly wasted and died, but not so quickly as after total destruction. The animals employed in the experiments were guinea-pigs.

Alezais and Arnaud, in a series of papers entitled "Recherches Expérimentales et Critiques sur la Toxicité de la Substance des Capsules Surrénales," conclude that the suprarenal capsule, though still functioning in the adult, is not indispensable for

life. Its unknown functions may be disturbed without any other results than a hyperpigmentation of skin and mucous membranes. But a lesion of the glands frequently induces death by affection of the nervous system. The pigmentation was confined to the mouth and nostrils, and the authors do not appear to be convinced that it was not accidental and independent of the lesion of the adrenals.

Hultgren and Andersson in 1899 published the results of a carefully conducted series of extirpation experiments upon rabbits, cats, and dogs. The effect varied very considerably in different animals.

In cats the unilateral operation (extirpation of one adrenal) never induced death, but, especially in old cats, there was some temporary disturbance of the general bodily health. Bilateral extirpation in these animals, whether carried out at one, two, or three sittings, led to death, without exception, in a few days. The average duration of survival after extirpation of both adrenals at one operation was 68 hours (nine cases); at two operations, 134 hours (eleven cases); at three operations, 88 hours (five cases), but in the last instance there were three cases of infection.

Extirpation of one and amputation of the other gland [1] in one sitting was generally very badly borne. Of the nine cats operated on in this fashion, only two survived any considerable time; one died in six hours, probably from the effects of the anæsthetic, and three in thirty to seventy-two hours. In these last the adrenal left behind had undergone necrosis. The three remaining animals died from various diseases within three weeks after the operation. It appears from these experiments that the removal of a large part of the adrenal tissue renders the animal more susceptible to infection.

Extirpation and amputation carried out at two sittings is less dangerous; out of thirteen animals so treated, two died from the actual operation, and three from necrosis of the adrenal left behind. The remaining eight all lived more than seven days, and of them two died of intercurrent diseases. If the removal of the glands be carried out at several operations, the length of time which elapses between the operations makes no difference to the result.

[1] In these "amputation" experiments a small portion only of one gland was left behind.

Hultgren and Andersson came to the conclusion that the resistance of castrated animals to adrenal extirpation is generally greater than that of normal animals. While, for example, normal animals survived complete extirpation at one operation for 61 hours, the corresponding time for castrated animals was 121 hours. In this relation the authors call attention to the striking morphological resemblance between the cells of the adrenal cortex and the interstitial cells of the testis and ovary.

In rabbits total extirpation of both glands at one operation is always fatal, and death occurs on the fourth or fifth day. If the operation is carried out at two sittings, the duration of life is considerably increased ; and three rabbits in which there was an interval of nine to fourteen days between the two operations lived 121 to 125 days, and were then killed while still in perfect health.

After extirpation of one and amputation of the other gland most of the rabbits lived a long time—as long as 320 days. The authors, immediately after stating this result, say : " Dieses Ueberleben der totalen Entfernung der Nebennieren beim Kaninchen is durchaus nicht durch die Anwesenheit wenigstens makroskopisch nachweisbarer accessorischer Nebennieren bedingt." Now, these cases were not cases of total removal of the adrenals, for some tissue of the amputated gland was always left behind. But perhaps this is meant to refer to the three cases of the previous paragraph, where the operation was performed in two sittings with an interval of nine to fourteen days between them. But apparently these were not cases of complete removal, for the gland was transplanted into the musculature.

Unilateral extirpation in rabbits produces no ill effects, and the same applies to dogs. Hultgren and Andersson only performed one total extirpation upon a dog, which lived six days.

The symptoms after removal of the adrenals were very characteristic. After the operation the animal recovers in a few hours, and in the first few days shows no ill effects from the operation, except some loss of appetite. During the last twenty-four hours before death, or earlier, the animal becomes stupid and quiet, and shows (especially is this the case with cats) weakness and uncertainty of movement in the hinder extremities. During this period, too, the temperature begins to fall, and the apathy and weakness increase. Then the hind-

limbs become stiff, the animals tire on the slightest exertion, and show extreme prostration. Finally, with increasing asthenia, there is dyspnœa, heart-weakness, and death. In rabbits convulsions are common, but do not occur in cats and dogs. The authors lay considerable stress upon the loss of weight which occurs even after the unilateral operation.[1] This symptom is less marked if the operation be carried out upon castrated animals. Fall of temperature, too, is regarded by them as a significant symptom. They could detect no change in the hæmoglobin of the blood, nor in the number of red and white corpuscles. They could detect no change in the electrical excitability of the nerves, and deny that removal of the adrenals gives rise to symptoms resembling those of poisoning by curare. There was no true paralysis, but only weakness and prostration. The operated animals were very sensitive to bodily movements. Adrenal extirpation has no effect on the protein metabolism. This applies, at any rate, to rabbits and cats. The Scandinavian authors consider it very probable that the adrenals have a varying functional significance in different classes of animals.[2]

Strehl and Weiss operated upon 114 animals, and found that total extirpation always causes death in from four hours to five days. If the operation was performed at two sittings, the second gland was always found to be enlarged. Among the symptoms noted by these writers after extirpation are muscular weakness, a low temperature, and a low blood-pressure.

Strehl and Weiss give the following tabular statement of their results :

Species of Animal.	Duration of Survival in Hours.	Number of Animals.
Dogs	22–75	7
Dogs	75–138	3
Cats	15–28	15
Cats	28–47	2
Rabbits	8–14	26
Guinea-pigs	4–9	20
Rats	15–19	4
Mice	8–13	10
Hedgehog	14	1
Weasel	21	1
Frogs	22–45	25

[1] This result was also obtained by Elliott and Tuckett, and has been frequently observed by the present writer.

[2] This is probably true of all the "ductless glands."

Biedl performed a series of experiments upon dogs, cats, and rabbits. These were carried out by a new method. In a preliminary operation by a lumbar incision the glands were "dislocated," the vascular connections were not severed, and the glands were stitched into their new position between the skin of the back and the dorsal musculature, so that they remained in a living condition and easily accessible extraperitoneally. After three or four days the glands were exposed by a skin incision, the vessels tied, and thus could extirpation be performed in the easiest possible manner.

It was found that extirpation of one gland produced no serious effects, but that after extirpation of both adrenals the animals died, almost without exception, in two to four days. Two rabbits which survived sixteen and twenty-eight days respectively were found to possess accessory adrenals on the vena cava beneath the renal veins.

As we have seen, Boinet succeeded in keeping rats alive for a considerable time after double epinephrectomy; and Harley many years ago found that the rat is able to withstand removal of both adrenal bodies. According to Wiesel, this is due to the fact that the rat normally possesses between the testis and epididymis accessory adrenals which are found to undergo compensatory hypertrophy after extirpation of the chief organs. These accessory bodies consist entirely of cortex (see p. 147).

In guinea-pigs a compensatory hypertrophy of accessory cortical bodies can be shown to occur, but this is never sufficient to keep the animal alive after complete removal of the main glands.

The case of the rat and the results of extirpation experiments upon this animal seem to point strongly towards the cortex being the part of the adrenal body which is essential to life. We shall, however, have to return to this subject again.

We see, then, that later work has confirmed in a general way the statements of Brown-Séquard as to the necessity for life of the adrenals. We cannot, however, altogether disregard the very considerable number of exceptions which have been recorded by various observers. Moore and Purinton report the survival of a goat for twenty-two days after complete removal of both adrenal glands, and they state that no accessory bodies could be detected.

According to Mayer, the diabetic puncture is ineffectual in

animals from which the adrenals have been removed. Further, in such animals the glycosuria resulting from extirpation of the pancreas is much reduced. Frouin states that the pancreatic diabetes is also much reduced in severity in animals from which one adrenal and two-thirds of the other have been previously removed. This matter will be referred to again in connection with the subject of adrenal glycosuria.

Levin reports that the blood of animals deprived of adrenals, when injected into another animal, raises its blood-pressure, but the tracing he gives indicates that the rise is not considerable. He hints that the substance which has this action may be something of a different nature from adrenin.[1]

F. The Question as to Accessory Adrenal Bodies in Relation to Extirpation Experiments upon Mammals

It will be seen, from a perusal of the section on the comparative anatomy of the adrenal glands, that not only may accessory adrenals consisting of both portions of the organ be present, but there may also be some glandules consisting of cortex only. The presence of chromaphil bodies and cells in different regions must also be borne in mind (Figs. 30–33). How far does the existence of these various bodies explain the discrepancies between the results obtained by different observers after adrenal extirpation? We know that some of the larger masses of chromaphil tissue (such as the parasomata of Zuckerkandl and the abdominal chromaphil bodies in various animals) contain adrenin, and this may have the same physiological purpose as that manufactured by the adrenal medulla, whatever that may be.

Schäfer recently exhibited a white rat operated upon by Harley some time between 1856 and 1858. This rat had the spleen and adrenals extirpated when it was only a month old and quite small. It increased in size after the operation quite

[1] According to Gautrelet and Thomas, after extirpation of the adrenals in dogs the heart contraction becomes weak, and the rhythm quicker, while the blood-pressure sinks after five hours to 6 centimetres Hg and later to 1 centimetre. The same authors report that in decapsulated dogs excitation of the splanchnic no longer induces glycosuria, as it does in normal animals. They further report that dogs and rabbits, after adrenal extirpation, become poikilothermic in that their body temperature, within certain limits, follows that of the external air, and that there is reduction of the excitability of the sympathetic. (See p. 235.)

as fast as its fellows which had not been touched. The animal was killed when five months old, and no discoloration of the skin or hair could be detected. The lumbar and other lymphatic glands were found enlarged.[1] Commenting upon this, Sir Edward Schäfer says: "The rat happens to be the one common animal which is able to withstand complete removal of both suprarenal capsules. The reason for this was not at the time apparent, although it is now known, for the rat is exceptional in possessing in various parts of the back of the abdomen and pelvis numerous small glandular structures which are composed of cells having the same characteristic features and functions as the cells of the suprarenal medulla."

But all observers have not been successful in keeping rats alive after double adrenal extirpation. Thus, H. and A. Cristiani found that in their experiments, unless a little of the medullary substance were left behind, the rats always died. From these experiments we should be justified in concluding that it is the chromaphil tissue (including the medulla of the adrenal body) which is essential to life. But, as we have already seen, Wiesel arrived at a different conclusion—viz., that it is the survival of accessory cortical substance which saves the animal's life. We thus see that the experimental evidence as to the effects of extirpation of the adrenals in the rat is somewhat conflicting, and the explanations offered by different observers as to the occasional or frequent absence of ill effects after extirpation are also conflicting. Moreover, it does not appear to be the case that the rat is more richly endowed with extracapsular chromaphil cells than are other common animals. The present writer has been so far totally unable to demonstrate any such tissue by the method of Stilling and Kohn, and is further informed by Dr. Kohn that there is, at any rate, no essential difference between the rat and other animals as regards its chromaphil tissues.

Vassale, who has performed a series of experiments with full knowledge of the anatomy of the chromaphil cells and their distribution in different animals, points out that the "paraganglion abdominale aorticum" is the most important mass of chromaphil tissue outside the adrenal body, and that

[1] This description is taken from the catalogue of the museum of University College Hospital, whence the specimen was borrowed by Sir Edward Schäfer for the purpose of his lecture.

it is always present, though in varying degree in the animals ordinarily used for experiment (dog, cat, and rabbit). The removal of one adrenal and the abdominal chromaphil body causes death in young cats with the same symptoms as those obtained after bilateral extirpation of medulla only. Vassale thinks that survival of animals, when it occurs after extirpation experiments, can be satisfactorily explained by the extra amount of extra-adrenal chromaphil substance which happens to be present in these individuals.

A further discussion of the question as to the relative importance to life of the cortical substance and the chromaphil material can only be carried on after the account of extirpation experiments upon lower vertebrate animals.

According to Biedl, the cortical accessory adrenals occur very rarely in dogs and cats, in rabbits in about 15 to 20 per cent. of animals examined, in rats in almost 50 per cent. of cases, in guinea-pigs not more than 4 per cent. of cases.

G. Extirpation of the Adrenals in the Lower Vertebrata

Perhaps the best-known and most-often-quoted series of extirpation experiments upon any animal is that carried out upon the frog by Abelous and Langlois in 1892. This was, of course, at a period before the discovery of the physiological effects of adrenal extracts upon the blood-pressure. The authors employed frogs because these animals, they say, do not suffer from the shock of operations as do mammals, and, in general, tolerate operative proceedings very well. Abelous and Langlois were the first to study the physiology of the adrenals in the frog.

Destruction by means of the actual cautery was the method of extirpation employed. A platinum wire brought to a red heat was applied to the bodies on the anterior surface of the kidneys. The authors found that male frogs are more suitable for the operation than female, and summer frogs better than winter frogs. There was never any post-operative shock.

Total destruction of both capsules always led to death. Immediately after the operation the animals were normal. It was only after a certain period that one observed ill-effects which finally caused death. The duration of survival was variable. It varied according to the season; winter frogs

might live twelve or thirteen days, but summer frogs never longer than forty-eight hours. On the other hand, if the winter frogs were kept at a mean temperature of 22° C., their period of survival was much diminished, and from twelve to thirteen days it was reduced to three.

The symptoms which followed destruction of both capsules consisted essentially in a progressive paralysis beginning in the hind-limbs, then becoming general and inducing death. On the day of the operation the animal remained well. It was as a rule at the end of the twenty-fourth to the thirtieth hour that symptoms came on. First one noticed a distinct inco-ordination in the movements of the hind-limbs when the frog jumped. Also the animals quickly became fatigued, and asthenia became more pronounced. This paresis affected first the flexors and adductors, and finally the extensors ; the frog was finally no longer able to respond even to the strongest stimulations except by way of the feeblest movements. Then the fore-limbs became affected, and the animal was completely inert. The respiration became slower and slower, and with contracted pupils the animal died.

If the animal were stimulated from time to time so as to provoke movements, it was found that the paralysis came on much more quickly, and the duration of survival was considerably shortened. From these facts the authors concluded that the length of survival was in inverse ratio to the chemical changes going on in the body. The more active these changes—as, *e.g.*, in summer frogs—the more quickly did death supervene.

Destruction of one capsule never induced death. The animals after such an operation showed no untoward symptoms, and their attitude and reactions were perfectly normal. Complete destruction of one capsule and destruction of the greater part of the other generally led to death, but the survival was always longer than after complete destruction of both. If the fragment left behind were of any considerable size, the survival was as long as in the animals in which only one gland had been destroyed. The insertion under the skin, in the dorsal lymph sac, of some fragments of kidney with the adrenals attached taken from a normal frog, prolonged the survival. Animals so treated might live twice as long as animals not so treated. The authors record that summer frogs were by this means

enabled to live five or six days. Post mortem it was found that the grafted capsules had disappeared—*i.e.*, the graft did not succeed. Injection of a saline extract of healthy glands only prolonged the survival by about twenty-four hours.

Now we come to some observations by Abelous and Langlois upon which they themselves laid considerable stress, and which have played a prominent part in all subsequent discussions on the functions of the adrenal bodies. They found that intravenous or subcutaneous injection of the blood of a frog dying after extirpation, into a frog recently operated upon induced rapid paralysis and death. The same injection into a normal frog only produces slight temporary symptoms. The authors were convinced that death after extirpation of both capsules is in reality due to the suppression of essential organs, and not simply the result of the shock of the operation. They further proved that the effects were not due to injury to the kidney. Their theory was that death resulted from the accumulation in the blood of one or several toxic substances of unknown nature, and that the suprarenal capsules are capable of the elaboration of a material which neutralizes the toxic effects of such substances. The toxic symptoms were stated to be those of curare-poisoning—paralysis, that is to say, of the connections between nerve and muscle.

These observations were in the main confirmed by Gourfein, who, however, could not satisfy himself that there was any difference between winter and summer frogs as regards the results of extirpation, and who denied also that the blood of operated frogs, when injected into others, gives rise to symptoms like those of curare-poisoning.

The same author also carried out a series of observations on pigeons and tritons. The pigeons only survived four to twenty-four hours if total extirpation had been performed; if only one-eighth to one-tenth of the organ remained behind, the animals lived fifteen days. Unilateral extirpation in tritons produced no symptoms. If only a speck of one adrenal remained behind, this was sufficient to keep the animal alive for from eighteen days to nine weeks.

Pettit was apparently the first to operate upon fishes. He performed a series of experiments upon the eel, having chosen this animal because its adrenals are placed on the ventral surface of the kidneys, a condition which is rare in Teleosts. He did

not, however, perform any total extirpations, since he was only interested in noticing a compensatory hypertrophy of one gland after removal of the other. This, he says, indicates a secreting function for the adrenal of the eel. Pettit looks upon this organ in the eel as the fundamental type of the suprarenal capsule, but he was apparently unaware that it consisted only of cortical substance.

Since the corpuscles of Stannius contained no chromaphil tissue, the Teleostean fishes appeared to offer an admirable opportunity of testing how far the cortical adrenal glands were essential to the life of the animal. Accordingly a series of experiments were performed by the present writer in 1898 upon eels. The results showed that an eel will survive the operation for a long time. The conclusion drawn was that the cortex of the adrenal is not essential to the life of the animal, but the discovery by Giacomini of the cranial cortical adrenal in Teleosts renders such a conclusion unwarrantable (see p. 103).

Biedl's experiments upon Elasmobranch fishes will be referred to in the following section.

H. The Question as to the Relative Importance to Life of Cortex and Medulla

We have seen that the extirpation experiments upon mammals have not definitely determined the question as to which constituent of the adrenal is essential to life, or whether, indeed, it is to the suppression of the compound organ in its entirety that we must attribute death after extirpation. Some authors believe that there is no special part of the organ which is of supreme importance in the pathology of Addison's disease, and consider that the adrenal bodies are single organs clearly essential to life, interference with which causes definite ill-results. Some, on the other hand, have concluded from experiments upon mammals that the medulla is the vitally essential constituent, although Wiesel came to the conclusion that the cortex is the part essential to life.

Biedl states that in mammals he has succeeded in removing the cortex, leaving the medulla behind intact, and that the operation was followed by the death of the animals. So he concludes that it is the cortex which is essential to life.

Biedl says that he has succeeded in determining for the

inter-renal of Elasmobranchs that after its extirpation the animals can live two or three weeks, and then die with symptoms of general prostration, just as do mammals after extirpation of both dual adrenals. Again, he concludes that the cortex is the essential part. These experiments upon Elasmobranchs must be very difficult, but so far they certainly seem to point to the cortex as the vitally essential tissue. The validity of these experiments is, of course, based upon the assumption that there is in Elasmobranchs nothing corresponding to the cranial cortical body discovered by Giacomini in Teleosts.

Some recent experiments carried out in my laboratory by Mr. T. D. Wheeler lend considerable support to the view that it is the cortex and not the medulla which is essential to life. Instead of attempting to remove the cortex and leave the medulla, Wheeler's object was to cauterize out the latter and leave the former. This was scarcely ever precisely achieved, but a systematic histological study of the glands after death showed that entire destruction of the medulla of both glands gives negative results. The only fatal cases (at any rate among the animals which could reasonably be supposed to have died of adrenal insufficiency) were those in which very considerable damage had been done to the cortex as well as to the medulla. In some cases the abdominal chromaphil body was removed as well as the adrenal medulla. Of course in such experiments groups of sympathetic chromaphil cells, as well as scattered cortical "accessory" bodies, must have been left behind. But this fact does not seriously affect the logic of the argument that it is the cortex which is essential to life. For, since removal of both adrenal bodies is fatal, and removal of the medulla is not, it follows that the cortex is the essential part of the gland so far as the maintenance of life is concerned. We have seen in a previous section that the cortex is the more important from a morphological standpoint.

It seems, then, that the symptoms observed in animals after adrenal extirpation, complete or partial, are by no means characteristic. The anatomical line which separates full physiological sufficiency from fatal insufficiency is very narrow. It has not been possible to produce experimentally any well characterized symptoms associated with partial adrenal insufficiency.

I. Changes found Post Mortem after Extirpation of the Adrenals

Reference has already been made to pigmentary changes after double extirpation (see pp. 141, 142).

Tizzoni reported severe lesions in the central and peripheral nervous system. He describes also extensive destruction of nerve fibres and ganglion cells, with marked congestion, alterations in the vessel walls, and hæmorrhages and leucocytal infiltration in all parts of the nervous system. But his work in this respect should be cautiously considered, for it must be remembered that he records death after removal of *one or both adrenals*, and this is opposed to the experience of every subsequent investigator.

Poll found in some cases among his rats after unilateral removal and transplantation, numerous reddish-black spots on the skin, but never on the mucous membranes.

Hyperæmia and hæmorrhages of the lungs have been observed after both the bilateral and the unilateral operation. Changes in other organs have only been noted by a few observers. Donetti states that he found changes in the nerve cells of the central nervous system of guinea-pigs and rabbits, especially in the medulla oblongata. The nuclei of the cells became vesicular, eccentric, and granular, and might disappear. He also noted changes in the nerve-cell body. Acute ulcer of the stomach has also been recorded.

Moore and Purinton record cardiac thrombosis following complete removal of the adrenals. The presence of ante-mortem clots in the heart has been observed on numerous occasions after adrenal extirpations in the laboratory of the present writer.

If the veins of both adrenal bodies be tied, the animal will survive for a much longer period than after double extirpation. But the operation is always fatal. The delay in fatal issue is due to a collateral circulation through the kidney.

J. Compensatory Hypertrophy of the Adrenals

Numerous authors have described a compensatory hypertrophy of one adrenal after the removal of the other. Thus,

Stilling found in rabbits, after extirpation of one adrenal, a considerable increase in weight of the one which was left behind. Pettit describes a similar hypertrophy in the cortical adrenal (" corpuscle of Stannius ") in the eel, after the removal of the glandule of the opposite side.

But all observers could not record such hypertrophy. It is probable that there is a difference in this respect between different species. Harley among the older workers, and Poll among the more recent, could not observe any such hypertrophy in rats. There can be no doubt whatever that such a compensatory hypertrophy may be regularly and easily observed in the dog.

The compensatory hypertrophy of accessory adrenals in the rat, which is described by Wiesel, has already been discussed. This may be related to the absence of hypertrophy on the part of the chief organ. A similar hypertrophy of the accessory adrenals which are found along the walls of the vena cava of the guinea-pig has been described by Velich.

According to some observers, the chromaphil cells, whether of the adrenal medulla or of the extra-medullary corpuscles, seem to be incapable of hyperplasia. If this really be the case, it is interesting to compare the fact with another to be referred to again later—viz., that in grafting experiments it is only the cortex which " takes "; the medulla disappears. It is possible that this lack of power of growth and of resistance to absorption is related to the high degree of specialization of the chromaphil tissues (Vassale).

That the functional capacity of one adrenal left after the removal of its fellow is not increased is the conclusion drawn after some experiments by Battelli and Ornstein. These authors removed one adrenal from dogs and rabbits, and let them live for from two to seventeen days. After this period the adrenin contents of the remaining gland were estimated by Battelli's colorimetric method in order to obtain a measure of the degree of vicarious function. No increase in the adrenin of the remaining gland, but rather a decrease, was found. These experiments, of course, have no bearing on the cortex of the organ, but only on the chromaphil medulla.

Elliott and Tuckett could not readily produce compensatory hypertrophy. They found that the English guinea-pig cannot survive the removal in one operation of a single gland. By

piecemeal extirpation a gland was successfully removed; the medulla of the gland left behind grew, and the cortex apparently not. But in a rabbit both cortex and medulla grew. This does not accord with the observations of Poll and Vassale. From some experiments carried out in my laboratory, I am inclined to believe that in dogs, after a large part of the adrenals have been extirpated, there is a notable compensatory hypertrophy of the abdominal chromaphil body.

K. Transplantation of the Adrenals

Although considerable attention has been devoted to the subject of transplantation of the thyroid, comparatively little has been done in this direction with the adrenal bodies.

Canalis appears to be the earliest worker who attempted adrenal transplantation. He grafted small portions of the adrenal into the kidney, but they became necrotic and were absorbed. Only once, fifteen days after the operation, did he find in the kidney scar the capsule of the adrenal and some of the cells of the external layer of the cortex.

Boinet transplanted adrenals intraperitoneally into rats. He observed atrophy and absorption, which, however, was sometimes delayed. He noted red spots on the transplanted organs, which he called "hémorrhagies capsulaires."

Gourfein reports that six days after the transplantation of frog's adrenal into the lymph sac of another frog the organ became decolorized, and attached by connective tissue to the muscles. After twenty days the decolorization and adhesions were more marked, and after forty days the gland was absorbed. When the adrenals of a guinea-pig were transplanted into the lymph sac of a frog there were adhesions, leucocytal infiltration of the gland, and inflammation of the surrounding tissue.

In all these experiments the effect was no more than that of the administration of a certain amount of adrenal substance in the form of the gland itself. The effects, if any, were purely chemical.

Poll was the first to make a systematic macroscopic and microscopic investigation of the transplanted gland. This author employed rats for his experiments. He removed the left adrenal body from behind, and in one series of experiments transplanted it into the dorsal muscles, in another series

beneath the skin of the back. In addition to some changes in the elements of the capsule, Poll records that the cells of the zona glomerulosa and the outer part of the zona fasciculata became changed into large polyhedral, at times pigmented, structures, which degenerated with the formation of fat droplets and pigment granules. The cells of the inner part of the zona fasciculata, the zona reticularis, and the medulla degenerate within the first week, forming a necrotic focus in the centre of the adrenal. This is absorbed in the course of the second week, and in connection with the process of absorption giant cells arise from the altered cells of the outer part of the gland. These finally disappear. Into the centre of the adrenal, at the place where the suprarenal vein leaves the gland, a band of connective tissue grows and develops, and remains permanently. In the course of the third week heaps of cells occur in the capsule, which resemble cortical cells, but possess only small compact cell bodies. These heaps fuse together, and grow into large masses having the form of a segment of a sphere. In these masses the small cells show signs of an arrangement like that of the zona fasciculata. In the interior, progressing outwards, begins a transformation of these cells into clear, finely reticular elements in all respects like cortical cells. Intramuscular implantation gives about twice as many successful results as subcutaneous. Favourable results were obtained only with young, small, and middle-aged animals.

It seems, then, that in all cases where the adrenals are transplanted the medulla disappears. This fact is, perhaps, not without significance as bearing upon the morphological relationship existing between the two constituents of the gland. The results of transplantation experiments are also of considerable importance in view of any future attempts to replace the adrenal function either in the human subject in Addison's disease or experimentally upon animals after extirpation of the organ.[1]

[1] Numerous experiments upon transplantation of different organs and tissues have shown that as a general rule the transplanted portions degenerate in a few months, even if they have made connection with surrounding tissues, and have undergone some temporary growth. Among the exceptions are portions of skin, thyroids, adrenals, and the notable case of Ribbert, who succeeded in grafting the rudiment of the mammary gland of a young guinea-pig upon the outside of the ear. The gland not only developed but ultimately secreted.

L. The Pharmacodynamics of Extracts of Adrenal Medulla (Chromaphil Tissues) and of Adrenin

1. *The General Physiological Effects of Chromaphil Tissue Extracts and of Adrenin*

It has already been noted in connection with the account of extirpation experiments that a few observers have obtained beneficial results after removal of the gland from administration of adrenal substance either in the form of the gland itself (grafts) or as watery or saline extracts.

In the present section we have to deal with the effects produced by the administration of the active principle to the normal animal. In the first instance we shall confine ourselves to the general effects (toxic) produced upon the animal as a whole, reserving the special effects upon different systems—*e.g.*, the hæmodynamics—for a subsequent section.

The earliest important investigations upon the effects of injecting adrenal extracts into animals are those of Foà and Pellacani. In their earlier experiments these observers employed aqueous solutions of fresh animal substances, including the adrenal body. They succeeded in causing death in a dog by injecting subcutaneously the adrenals of a calf in the form of neutral extract. Similar but more rapidly fatal effects were obtained in experimenting upon guinea-pigs and rabbits, but when injected intravenously they obtained like results from extracts of liver and kidney. So they concluded that the effect was not a specific one.

In their later work, the Italian observers eliminating the injurious effects of fibrin ferment in their extracts, found that the toxic action was specific for the adrenals. They further determined that the toxicity is not due to the acids present, for if one separates these out the extracts remain active. Further, the toxic effects are not due to a ptomaine which the authors found in the glands, for this is physiologically inactive. They conclude that the active principle of the adrenals paralyses the spinal cord and the medulla oblongata, destroys completely all motion and sensation, and kills by paralysis of the respiratory centre. These authors prepared their extracts by boiling, evaporating to dryness,

extracting in the cold with alcohol, and redissolving in water. "After filtering and evaporating the aqueous solution, one obtains a residue coloured black, of a peculiar odour, of very acid reaction, and which, in a dose of 1 gramme, kills a healthy dog." Thus it will be seen that the doses employed corresponded to very large quantities of the fresh gland substance.

These experiments were adversely criticized by Alexander, who suggested, with considerable justice, that chemical changes might have taken place in the active principle during the complicated manipulations employed by the Italian observers. This or some such opinion has been shared by numerous observers.

Oliver and Schäfer injected subcutaneously comparatively large doses of aqueous adrenal extracts into the dog, the guinea-pig, and the cat without obtaining any very obvious effects. But in the rabbit a large dose of adrenal extract administered subcutaneously invariably produced death. Among the symptoms noted was a very low temperature. In frogs the symptoms were those of paralysis due to the action of the poison upon the central nervous system. The animals recovered from large doses in a comparatively short time.

Gluzinsky, injecting intravenously, obtained paralysis of the posterior part of the body, and convulsions in the anterior part, with acceleration of the respiration and dilatation of the pupil. The animal succumbed amid progressive dyspnœa and general paralysis.

Dubois attempts to account for the variations in the effects obtained by classifying them under three heads: (1) Those depending upon the animal experimented upon; (2) those due to the animals from whose glands the extracts were made; and (3) variations conditioned by the mode of obtaining the extracts. He found that fatigue previous to injection rendered the animal much more susceptible to the toxic action, that extracts obtained from the glands of wild animals were more powerful than those obtained from animals which had been kept in captivity, and that the medullary region was much richer in the active poison than the cortex.

The present writer in 1897–98 performed a series of experiments upon rabbits, guinea-pigs, rats, mice, frogs, toads, as well as upon dogs and cats. The fresh-chopped glands were boiled with normal saline solution, and the extract filtered,

or the fresh glands were pounded with water or normal salt solution and sand in a mortar, and the filtrate injected without boiling. Dried material was also sometimes employed for the preparation of the extracts. Sometimes cortex and medulla were carefully separated, and separately used for extracting and injecting, either by the fresh or the dry method. In addition to the above, glycerin and alcoholic extracts were employed.

In most of the experiments the injection was made subcutaneously beneath the skin of the back with a hypodermic needle. In some cases the extract was injected into the pleura or the peritoneum, and in a few cases into a vein. Numerous control experiments were performed.

The adrenals employed in the making of the extracts were obtained mostly from the sheep, but some were taken from the ox, and occasionally those of smaller animals were used—*e.g.*, dog, cat, rabbit, guinea-pig, etc.

The conclusions reached as a result of this series of experiments were as follows: In rabbits, guinea-pigs, rats, mice, frogs, and toads, after sufficiently large doses of adrenal extract injected subcutaneously, we get slowed muscular movements, paresis, and finally paralysis of the limbs (hind-limbs always becoming affected first), bleeding from the mouth and nostrils, hæmaturia (not observed in rabbits), breathing rapid and shallow at first, finally becoming deep and infrequent, and occasionally convulsions resembling those of asphyxia preceding death, before which the temperature often falls very low. The paralysis is central. The effects are due to the medulla of the adrenals, the cortex containing no toxic substance. The effects are specific for the adrenal, and not common to other glandular extracts. The toxic material is easily eliminated in some way or other. This accounts for the large dose required to produce a fatal result, and accounts also for the ease with which recovery takes place. Idiosyncrasy plays a large part in the conditions. A partial immunity can be set up by giving doses not sufficient to kill. This immunity passes off after a few weeks.

In dogs the first effect of a subcutaneous injection of an adrenal extract is excitement. There is increased muscular activity, which passes into a stage of agitation with tremors, until paresis and finally paralysis come on. Thirst is also a

striking symptom in dogs. There is abundant micturition, but no hæmaturia.

In cats by far the most noticeable result of the injection was an enormously increased rapidity of the respiratory movements in the early stage. Thirst and loss of appetite were recorded, but the paralysis was not so definite as in other animals. In the cat doses sufficient to kill do not raise the blood-pressure within half an hour of injection beneath the skin.

The remote effects noted by Foà and Pellacani, as well as by Oliver and Schäfer, were not noticed in this series of experiments. If the dose were sufficiently large to produce any effects at all, there were some changes in reaction and disposition within a few minutes.

After it had been shown by experimental evidence (Vincent) that the "paired suprarenal bodies" ("medullary" or "chromaphil bodies") and the inter-renal gland of Elasmobranch fishes correspond respectively to the medulla and the cortex of the adrenal body of the higher vertebrata, and that the "corpuscles of Stannius" of Teleostei consist solely of "cortical" substance, it appeared to be a matter of some interest to test the effects of the two kinds of tissue in Elasmobranchs and of the cortical bodies of Teleosts when extracts of them are injected subcutaneously into small animals. Naturally, only very small quantities of material could be obtained for this purpose, but the effects upon mice were quite definite. The "corpuscles of Stannius" obtained from six specimens of the codfish (*Gadus morrhua*) were found to weigh in a moist state 0·4 gramme. These were extracted by boiling with a normal saline solution. The filtered extract was then injected beneath the skin of the back of a mouse. No effects whatever supervened. Next, the "paired suprarenals" of Balfour ("chromaphil bodies") from seven specimens of *Scyllium canicula* were found to weigh, when moist, 0·3 gramme. These were similarly extracted, and the filtrate administered to the same mouse (which had remained in perfect health) a few days later. The animal was immediately and powerfully affected. The breathing became very rapid, the limbs became weak, the temperature lowered, and death with convulsions ensued in less than five minutes. Extracts of the elasmobranch inter-renal gland produced no effects when injected in the same

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manner. A further experiment with material obtained from *Raja clavata* gave harmonious results.

These experiments gave further positive evidence of the homology of the "paired bodies" of Elasmobranchs with the medulla of the mammalian adrenal, and, in conjunction with the morphological and histological evidence as to the homology of the "inter-renal" and the "corpuscles of Stannius" with the cortex of the mammalian adrenal (Vincent, Balfour, Diamare), show that the toxic effects of subcutaneous administration of adrenal extracts are obtained only with chromaphil substance, whether forming the medulla of the adrenal or the paired chromaphil bodies of Elasmobranch fishes.

An important observation was made by Blum in 1901. After subcutaneous or intravenous injection of adrenal extracts, glycosuria occurs, even when the animals injected are being fed upon a diet free from carbohydrates, or after several days' inanition, when it is to be supposed that all the glycogen must have disappeared from the liver.[1] The author considers that the function of the adrenal is to free the organism from the poisonous products of metabolism.

More recently the purified active principle of the chromaphil tissues (under various names, perhaps most commonly "adrenalin") has been employed for subcutaneous and other modes of injection instead of the crude extracts. The results have not been very different from those obtained when extracts of adrenal medulla were used.

The immunity first observed by the present writer, working with adrenal extracts, has been recently recorded by Ssaweljew, who employed pure adrenin. Waterman has succeeded by injecting rabbits with larger and larger doses of *r*-suprarenin in bringing the animals into a condition in which they cannot be rendered glycosuric by means of *l*-suprarenin.

Since Blum's original communication numerous papers upon adrenal glycosuria have appeared, and the majority of workers have used, not extracts of the adrenal or of chromaphil substance, but the pure active substance (adrenin). Lazarus states that after prolonged administration of adrenin there is marked hypertrophy of the islets of Langerhans, of the pancreas, as well as of the adrenal bodies. Herter and

[1] More recent observers conclude that the glycosuria lasts until the glycogen store of the liver becomes exhausted.

Richards, and also Paton, confirmed Blum's observation that, as with phloridzin and pancreatic diabetes, glycosuria occurs even when stored carbohydrates have been previously eliminated. Later observers have not held this view. As pointed out by Schäfer, there seem to be connecting links between the glycosuria set up by pancreatic removal and that due to the action of adrenalin. Herter and Wakeman found that quite small amounts (1 c.c. of a 1 in 1,000 solution) of adrenalin applied to the pancreas provokes marked glycosuria.

According to Mayer and Frouin, as already noted (*vide supra*, p. 146), neither the puncture diabetes nor pancreatic diabetes occur after extirpation of the adrenals. Zuelzer has gone so far as to assign definitely an adrenal origin to the pancreatic diabetes of Mehring and Minkowski. He found that extirpation of the pancreas carried out at the same time as ligature of the adrenal veins provokes little or no glycosuria. Injection of certain doses of adrenalin remains without effect if one injects at the same time a dose of pancreatic extract. In dogs, if the pancreas and the adrenals are simultaneously extirpated, there is no glycosuria. Zuelzer also made some experiments with an artificial circulation through the liver. He concludes that the adrenal secretion is normally neutralized by the pancreas, and that pancreatic diabetes is really a "negative pancreatic diabetes," while it may be regarded as a "positive adrenal diabetes," the real stimulus to the genesis of glycosuria being the adrenal secretion.

Similar views are held by other writers. Others again connect the adrenin glycosuria with the functions of the thyroid and the action of the sympathetic nervous system (Eppinger, Falta, and Rudinger).

Loewi reports that in diabetes arising after extirpation of the pancreas adrenalin produces dilatation of the pupil if applied to the conjunctiva, whereas it has no influence on the normal eye. This observation was confirmed by Biedl, and it is stated that this reaction may be used as a diagnostic sign of pancreatic diabetes.

In 1898 Biedl discovered a new form of experimental diabetes. This was induced by tying the thoracic duct or by leading it to the exterior and allowing the lymph to flow away. The author considers that the lymph which constantly flows into the circulation from the lymphatic duct contains a

substance which influences directly or indirectly the supply of sugar in the organism. Biedl and Offer find that in this form of diabetes also the pupil reacts to adrenalin dropped on the conjunctiva. They further find that admixture with lymph or simultaneous injection of lymph from another animal prevents both the adrenin diabetes and the mydriatic reaction. In this relation Schäfer recalls the observation of Lépine that in pancreatic diabetes the injection of lymph from a normal animal produces marked temporary diminution of sugar in the urine. He suggests that the lymph normally contains a chemical (glycolytic ?) substance, derived from the islets of the pancreas, which substance is essential to the due maintenance of normal carbohydrate metabolism. This whole question has recently been complicated by Pflüger's announcement of a "duodenal diabetes" (*vide supra*, p. 40). It seems possible that the final solution of the problem may be arrived at by an accurate knowledge of the interaction between the adrenals and the pancreas through the mediation of the sympathetic nervous system.

Meltzer found that subcutaneous injections of adrenalin, which normally are without effect on the pupil, produce marked dilation after removal of the superior cervical ganglion.

Underhill and Closson could not find any change in the nitrogen of the urine in adrenin glycosuria, such as was recorded by Paton.

It is stated that heat polypnœa hinders the onset of adrenin glycosuria, while warmth alone does not. This result appears to depend on the destruction of the adrenin by the increased chemical processes of the body, due to the polypnœa.

Drummond reports that after administration of adrenalin there occur congestion of organs and histological changes, indicating that the substance acts as a protoplasmic poison.

Oliver and Schäfer suggested that the material obtained from the adrenal medulla, which produces death, is of a different nature from that which has such a powerful effect upon the blood-pressure. The paralysis is due to the action of the poison upon the central nervous system. The present writer came to the conclusion that the adrenal body contains an active principle which acts both centrally and peripherally. The central action is produced most probably upon the motor centres of the brain, while the peripheral action is shown by

the effect upon blood-pressure when the extract is injected intravenously. The question naturally arises whether both these effects are due to one substance or whether there are two active materials present in adrenal extracts. It seems to be generally admitted at the present time that the toxic effects, like those on the blood-pressure, are due to the action of adrenin. If this be the case, it would seem that this substance has a central as well as a peripheral action.

Elliott discusses the effects of subcutaneous injections of adrenin, and classifies the possible causes of the symptoms under three heads : (1) The strain thrown upon the circulatory system by the great rise of blood-pressure ; (2) a poisoning of tissues by quantities of adrenin exceeding that sufficient for physiological stimulation ; (3) the poisonous action of possible decomposition products of adrenin within the body. The author considers that the chief cause is No. 2—*i.e.*, that the excess of adrenin itself is toxic. He points out that a poisonous action of adrenin on bioplasm is suggested by its chemical constitution, which displays the $-NH.CH_3$ grouping that resists chemical alteration in the body with great stubbornness.

Ssaweljew, as we have seen, confirmed the observation of the present writer that some immunity can be established by administering doses of adrenin not sufficient to cause death. But he reports further that he could obtain an immune serum which was capable of conferring passive immunity upon a second animal. Stradiotti, employing the "paraganglina Vassale," produced in dogs a serum which could precipitate the "paraganglina" and neutralize its power of vasoconstriction. Elliott and Durham point out that these results are not in accordance with expectation, for as yet no instance has been discovered of the production of an antibody to a substance of such chemical character as that of adrenin. In their experiments no trace of an anti-adrenin could be found.

2. *The Special Physiological Effects of Chromaphil Tissue Extracts and of Adrenin*

1. *The Effects upon the Heart and Arteries.*—A new stage in the history of our subject was reached in the year 1894 by the discovery of Oliver and Schäfer that extract of the medulla of the adrenal bodies produces a very remarkable

rise of the blood-pressure on injection into the circulation of a living animal.

These observers employed glands mainly from the calf, but also from the sheep, the guinea-pig, the cat, the dog, and man. The physiological effects noticed were identical in all, the only difference being in the case of diseased adrenals in man (Addison's disease), in which case, if the disease were extensive, no effect whatever was obtained. Extracts of the glands were prepared with water, with alcohol of various strengths, with glycerin, with ether, nigröin, and various other solvents. They were made either by digesting an ascertained weight of the fresh gland or of the dried gland in these menstrua, or in addition by boiling the infusion for a few minutes. The animals experimented upon were chiefly dogs, but some experiments were also made upon cats, rabbits, and guinea-pigs, and one upon a monkey. The extracts were usually administered by intravenous injection, and the effects upon the arterial system determined by the mercurial kymograph, various kinds of plethysmographs, and perfusion through the arterial system of the frog, after the nervous system had been destroyed.

The chief and fundamental effect noticed was *contraction of the arterioles.* This contraction is so great as to produce (even when concomitant vagus action has caused a great diminution in the rate and force of the heart's beats) a *large rise of blood-pressure,* and, in the case of the frog with its nervous system destroyed, almost complete cessation of the flow of circulating fluid through the arterioles.

The usual effect of the injection is to produce constriction of isolated organs. The limb shrinks (Fig. 39), the kidney and spleen contract considerably, while the heart and larger bloodvessels are enormously distended. But sometimes a limb expands, and in some experiments one limb contracts while another expands. In the later stages of experimentation the passive dilatation is more usual. Hoskins, Gunning, and Berry have recently reported that adrenin causes active vasodilation of the muscles, while it gives rise to constriction in the cutaneous vessels. Removing the skin from a limb converts the usual contraction into an expansion. The rise of blood-pressure is very largely due to constriction of the splanchnic arterioles. But sometimes the intestine expands

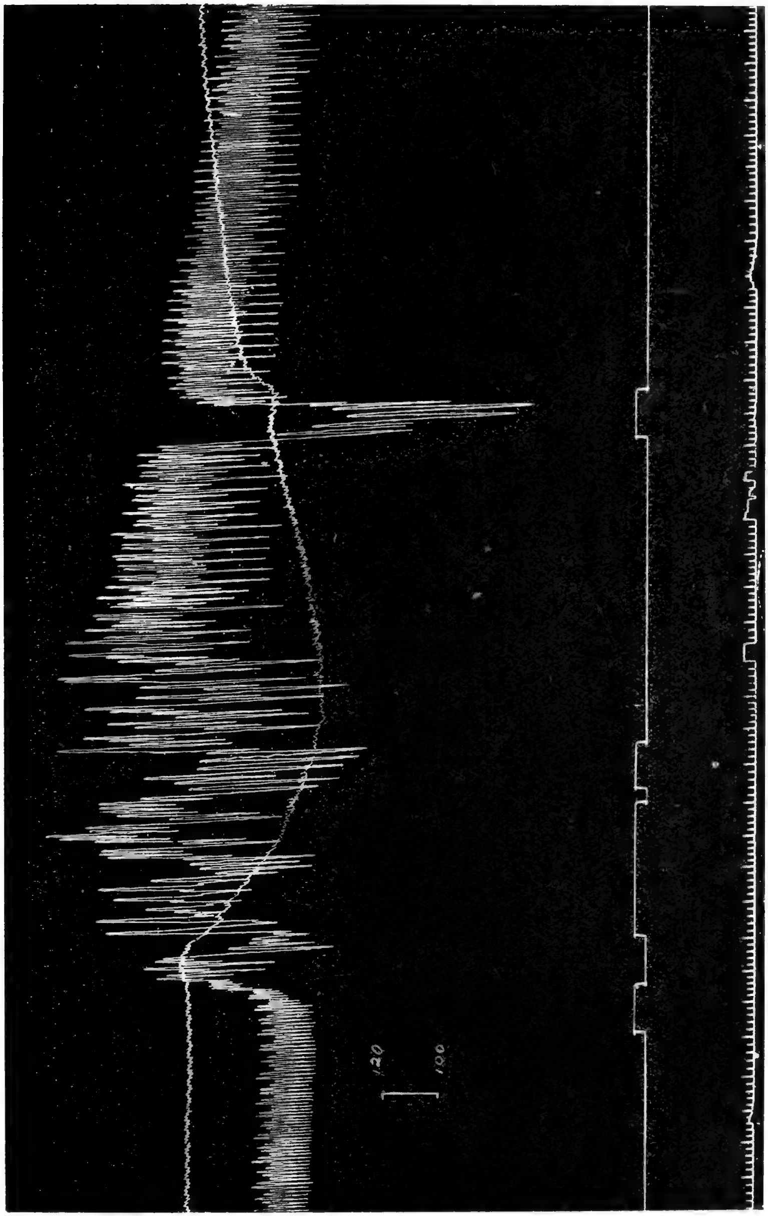


FIG. 39.—Tracing showing the effect of injection of 0·01 gramme of adrenal extract into a vein of a dog weighing 15 kilogrammes. Ether and morphine. The lower curve is that of the carotid blood-pressure, the upper one that of the volume of the left-hind-limb. At the second and third signals the vagus was stimulated.

(see Fig. 42). In some cases Oliver and Schäfer noticed in organs enclosed by a plethysmograph an apparent struggle between the diminution in size resulting from contraction of the arterioles and the expansion due to swelling of the larger bloodvessels, and some of their curves show a passive dilation at the beginning of the effect of an injection, followed by a prolonged diminution in size due to a more marked contraction of smaller arteries having supervened. The medium-sized arteries also participate in the dilation.

The contraction of the arterioles occurs in a frog with its nervous system destroyed, as stated above. It also occurs after section of the spinal cord and after section of the nerves going to the limb. Therefore the contraction must be due to the direct action of the active principle of the adrenal medulla upon the muscular tissue of the bloodvessels. This question as to the precise tissues upon which adrenin acts will be referred to again later on.

The rise of blood-pressure occurs after a certain interval of latency (twenty seconds in the dog) occupied by the passage of the extract from the vein into the arteries. The rise takes place, whether the vagi be cut or not, and whether atropin has been injected or not. But it is much greater after section of the vagi or after injection of atropin, because of the concomitant effect of the injection upon the cardiac inhibitory centre in the medulla (see Fig. 41). The rise is rapid, but only lasts a few minutes. During the rise the Traube-Hering curves are abolished, and in the cat and the rabbit the effect of stimulation of the depressor nerve is in abeyance. Sometimes a rise followed by a fall is obtained, and sometimes a pure fall. These effects will be referred to again later.

But the rise of blood-pressure is due not only to constriction of arterioles, but also to *increased rate and energy of the heartbeat.*

Another striking phenomenon noticed by Oliver and Schäfer was *cardiac inhibition through the vagi.* Sometimes in the earlier stages of the action of the extract, the heart, instead of being augmented and accelerated, is strongly inhibited. When the vagi are cut or atropin administered, this effect is abolished, and the constriction of the arterioles, combined with the augmentation of the heart, produces an enormous rise of the blood-pressure. The cardiac inhibition is of central origin, but the augmentation is due to the direct action on the heart. Some-

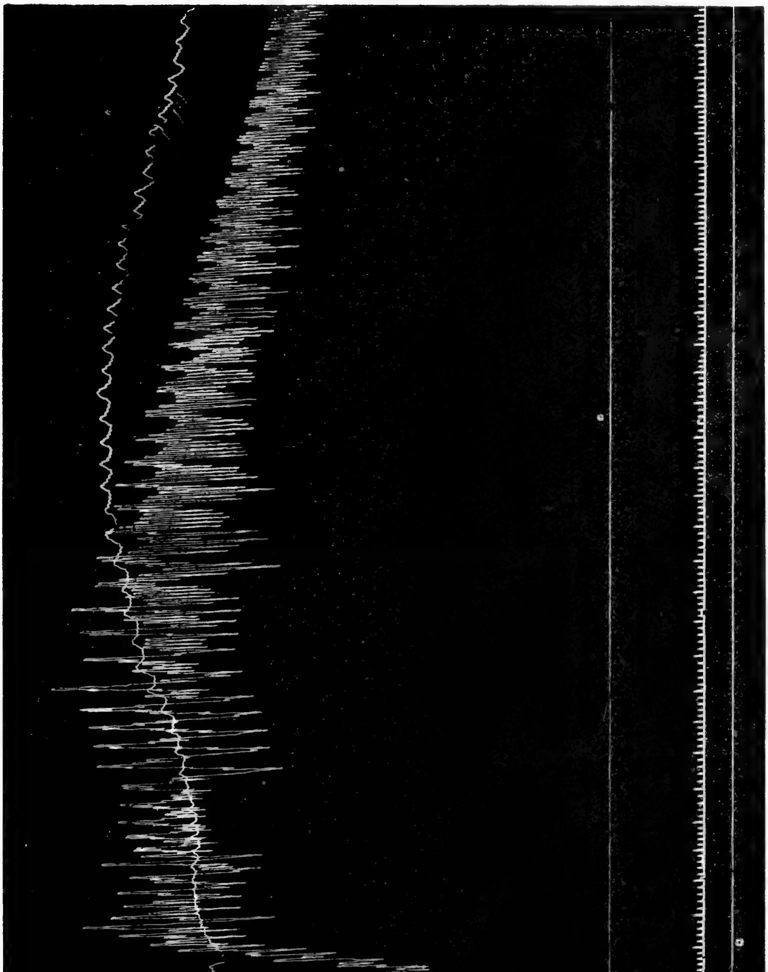


Fig. 40.—Tracing showing the effect of the injection of 0·005 gramme nicotine into a vein of a dog, 13·5 kilogrammes. Lower curve indicates carotid blood-pressure, upper one is the volume of intestinal wall. *Cf.* this with Fig. 39. Ether and morphine.

times the inhibitory effect is shown only after a few minutes. The effects obtained with the isolated frog ventricle were less striking than those in mammals.

Finally, it was proved by these authors that extracts of the cortex of the gland are quite inactive, the *active principle being confined strictly to the medulla.* Their general conclusion was that the medulla of the adrenal secretes a material whose action is to increase the tone of all muscular tissue, and especially that of the heart and arteries.

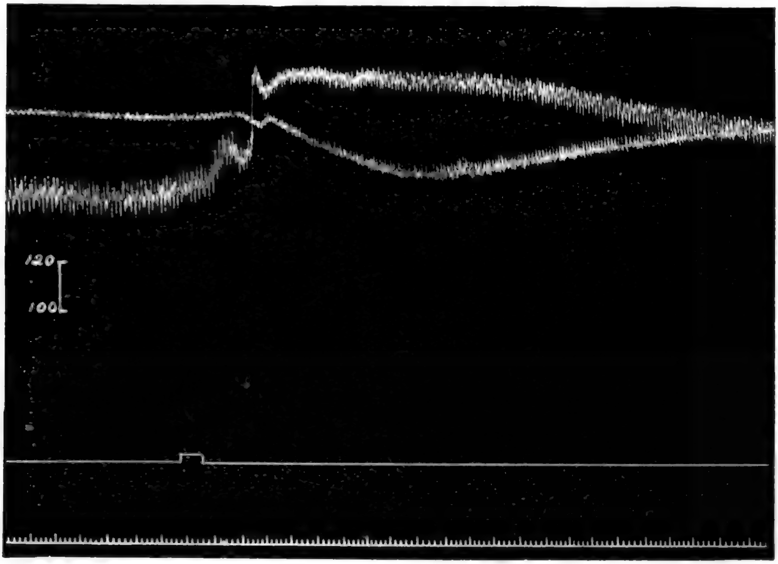


FIG. 41.—Tracing showing the effect of adrenalin after previous administration of a dose of atropin. Dog, 15 kilogrammes. Ether and morphine. Lower curve is that of the carotid blood-pressure, upper one the volume of the left hind-limb.

The work of Oliver and Schäfer was confirmed in its main outlines by Cybulski and Szymonowicz. The Polish physiologists independently observed many of the same phenomena, and brought corroboration of many of the observations. But in some details and upon one important point they obtained different results; they considered that the extract produces its vasoconstriction effects not peripherally, but centrally upon the medulla. This was, as has been proved by all subsequent investigations, an erroneous conclusion.

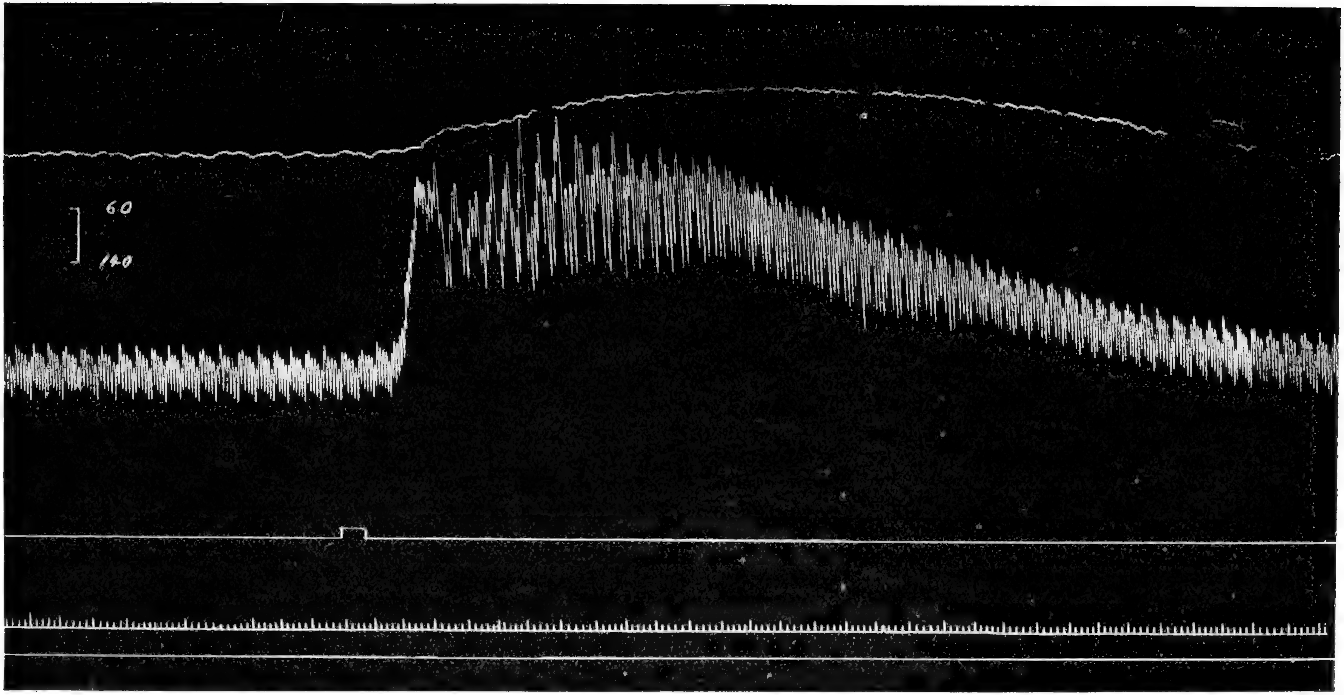


FIG. 42.—Tracing showing the effect of injection of adrenal extract after previous administration of nicotine. Dog, 13·5 kilogrammes. Ether and morphine. Upper curve shows volume of intestinal wall.

As we have already seen, the effects can be induced in an animal from which the central nervous system has been completely removed.

So far as the hæmodynamic effects of adrenal extracts are concerned, the papers of Oliver and Schäfer gave an accurate account of all the fundamental facts, and there is little or nothing to add to their account up to the present time.

It had been shown by Gourfein and by Cybulski that adrenal extract in sufficient dose paralyzes the vagus (see Figs. 39 and 43). This was confirmed by Langley. The paralysis is brief. In the cat 5 to 10 c.c. of 1 per cent. extract of dried adrenal cause, as a rule, paralysis for from thirty seconds to one or two minutes. When a dose is given a little short of that required to make stimulation of the vagus ineffective, the respiratory curves disappear, and there is a gradual fall of pressure. This result is probably due to weakening of the heart-beat without much variation in rate.

According to Oliver and Schäfer, injection of extract in the dog after section of both vagi causes only quickening of the heart-beat. In the cat Langley found that after section of the vagi adrenal extract sometimes causes quickening only, but that sometimes the rate is irregular, and in one case the heart stopped for three minutes. The slowing, when it occurs, is, Langley thinks, due to the increased work thrown upon the heart; whether the action is entirely direct on the heart muscle or is partly due to a post-ganglionic axon reflex, there is hardly sufficient evidence to show, but the slow beats caused by the extract are fewer or absent after injection of nicotine, although the rise of blood-pressure is commonly higher.

As pointed out by Oliver and Schäfer, the extract does not act equally on all the arteries; its effect is perhaps greatest upon those of the splanchnic area, and its action in general runs parallel with the action of the sympathetic nerves on the bloodvessels. Thus, injection of adrenal extract causes great pallor of the uterus and but little of the bladder. It has a strong action on all skin arteries and on all medium-sized arteries in the body. In the abdominal viscera its effect is great on the main branches of the cœliac and superior mesenteric arteries.

The primary effect of adrenal extract on the vessels of the submaxillary gland is constriction. The gland becomes pale

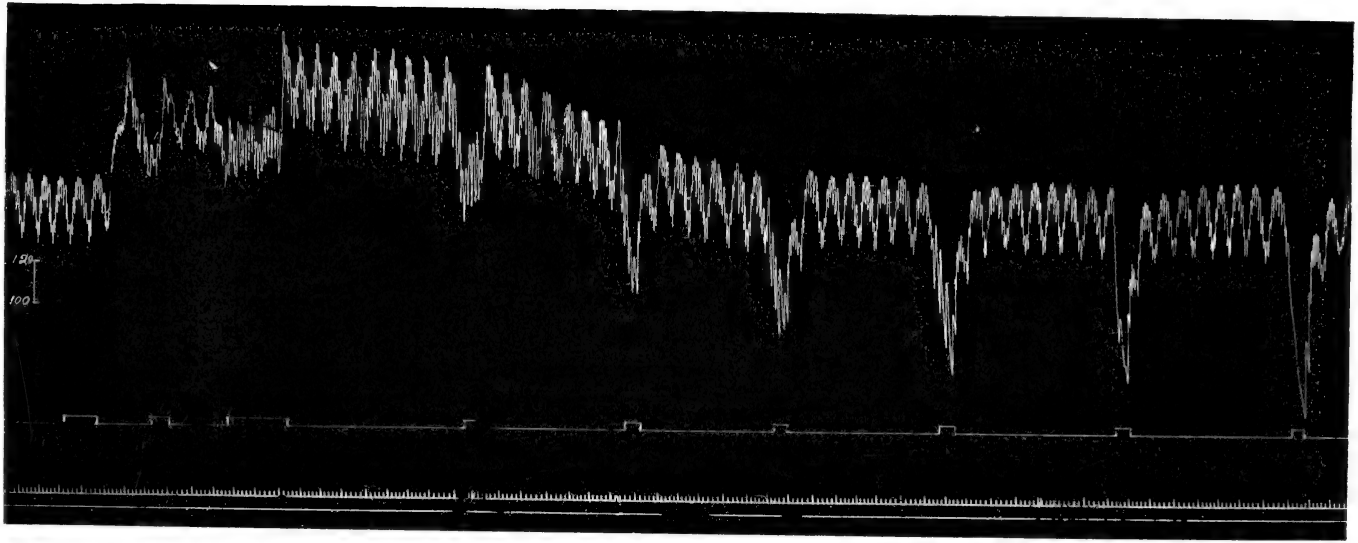


FIG. 43.—Tracing showing the paralyzing effect of adrenal injection upon the vagus nerve. The nerve was stimulated at the points signalled during the height of the blood-pressure, and at various points during the fall. It is seen that when the blood-pressure is at its highest point, stimulation of the vagus produces practically no effect. This effect becomes gradually more marked as the pressure falls, till on the last occasion of stimulation the effect obtained is the normal one.

and remains so for thirty seconds. Then it becomes flushed, and the flushing lasts longer than the secretion caused by the injection. The pallor is not so great as that produced by stimulating the cervical sympathetic, nor is the flushing so great as that produced by stimulating the chorda tympani. Both of these nerves have their usual action on the blood-flow, if stimulated while the secretion is going on.

In the dog pallor of the bucco-facial region is produced by adrenal extract. This is the effect produced by weak stimulation of the cervical sympathetic (Langley).

Brodie and Dixon were unable to obtain evidence of constriction of the pulmonary vessels on injection of adrenalin, and thought this was because the pulmonary arterioles possess no vasomotor nerve-supply. (Adrenalin, they considered, acts on the nerve endings.) Plumier, using larger doses, succeeded in getting a positive result—that is to say, he recorded some constriction of the pulmonary vessels on injection of adrenalin ; but, according to Schäfer, the action is far less than upon the sympathetically innervated vessels.

It was stated by Spina that the injection of adrenal extract causes reddening of the brain, so that the peripheral vessels were not constricted, but Wiggers, using the isolated dog's brain and perfusion with Locke's fluid containing adrenalin, has been able to observe a diminution of the outflow of fluid, from which he concludes that the brain possesses vasomotor nerves, and that adrenalin acts on the ends of these. As for the coronary vessels, it is usually stated that adrenin does not constrict these. Schäfer correlates this with the absence of vaso-constrictors from the cardiac accelerators, and concludes that, with both forms of excitation, quickening of the flow through the coronaries was brought about. It may be supposed, however, that heart muscle is dilated by adrenin just as skeletal muscle is. Elliott suggests that in the beating heart such an action cannot be dissociated from a possible secondary dilatation by metabolites from the increased work of the heart muscle. He states that when perfusing a strip of the cat's ventricle by a single coronary artery he has seen almost instant increase of flow after addition of adrenalin to the Locke's solution used. This occurred with a strip that did not beat, and therefore independently of muscular metabolites. Langendorff has recently immersed strips of the vascular wall attached

to a lever in adrenalin solution ; he states that whereas strips from the arteries so tested contract when adrenalin is brought in contact with them, a strip from a coronary artery will become relaxed, and he infers from this that adrenin produces inhibition and therefore vasodilation. Langendorff points out that from a teleological standpoint this is advantageous ; since the adrenin increases the force of the heart-beat, it must be favourable for this action that the calibre of the vessels in the heart-wall becomes increased. Schäfer has, however, not succeeded in obtaining the result described by Langendorff, and suggests that possibly there might have been some other substance than adrenin in the solution used. According to some recent experimental investigations carried out by Barbour and Prince, adrenin actively dilates the coronary vessels in the dog, cat, rabbit, ox, sheep, and pig, but constricts them in man and the monkey.

Moore and Purinton recorded a *fall* of blood-pressure instead of a rise when very small doses of adrenal extract are administered. Other authors have from time to time made reference to a depressor constituent of the adrenal. This is not to be wondered at when we remember that, as first noted by the present writer, extracts of tissues generally lower the blood-pressure ; but the presence of a depressor constituent will not explain the result obtained by Moore and Purinton, for there is no apparent reason why the depressor effect should not be swamped by the pressor with small, just as with larger, doses. Pari finds that with freshly prepared extracts there is never a lowering of the blood-pressure, but that with very dilute solutions, which have been kept for some time, this may sometimes be observed. He suggests, therefore, that the depression described by Moore and Purinton was due to chemical changes in the adrenalin in the dilute solution. Pari supports the view of Hunt, that the depressor substance is choline. The matter has recently become of considerable theoretical importance as bearing upon current theories of the function of the chromaphil tissue (see p. 216). Sometimes one obtains, after a preliminary rise, a fall of blood-pressure, even with moderately large doses of adrenin. This occurs especially in my experience with certain commercial preparations when the blood-pressure is high before the adrenin is administered. The fall of blood-pressure with small doses is admitted

by many workers as a regular phenomenon. It is found that the splanchnic arteries are constricted while the peripheral are dilated with very small doses. But with such doses the dilation of the peripheral vessels begins earlier and lasts longer than the constriction of the splanchnic. The result is that the splanchnic rise is masked by the peripheral fall (Hartman).

It has been mentioned above that the "paired suprarenal bodies" of Elasmobranch fishes yield an extract which produces the same physiological effects as adrenal medulla. In 1898 Langlois showed that the adrenals of the frog (which contain masses of chromaphil cells) contain an analogous substance and are functionally homologous with the glands of higher vertebrates. Biedl and Wiesel proved that the "Nebenorgane" of Zuckerkandl contain the active substance. The present writer has further shown that the "abdominal chromaphil body" of the dog also contains the pressor substance, and Fulk and Macleod that the retroperitoneal tissue of various animals contains substances having the same effect on intestinal and uterine muscle as adrenin. Mulon has raised the blood-pressure of an animal by injection into the circulation of an extract made from the carotid body of the horse (which body was shown by Stilling to contain chromaphil cells). It seems clear, therefore, that all chromaphil tissues, whether contained in the adrenal or not, yield adrenin, or a substance having similar chemical and pharmacodynamical properties.[1] How far this conclusion may be adduced, in conjunction with other observations, as evidence of an internal secretion on the part of all these tissues, is a matter for subsequent consideration (see p. 237).

A pathological effect which has been noted by Josué as a result of repeated injections of adrenin into the auricular vein of the rabbit is a degenerated condition of the wall of the larger arteries, especially of the aorta (arterio-sclerosis). Atheroma, calcification, and even aneurisms are also described, and the changes have been recorded in the pulmonary and other arteries. It is said that these effects are not peculiar to adrenin, but are produced by other blood-pressure raising

[1] Of course, this conclusion is based upon the provisional assumption that "chromaphil" tissues are specific in their nature, and are everywhere of the same essential character. It is not out of the question, however, that there may be some cells which stain brown with bichromate, which are, nevertheless, of a different character.

substances, such as digitalin and nicotine. According to Elliott, "mechanical strain is doubtless the cause of the atheromatous lesions which develop after repeated intravenous injections. These occur in the coronary arteries which are not contracted by adrenin, and must, therefore, be widely distended in the general rise of blood-pressure" (see p. 175). But Batty Shaw is of a different opinion. He states that if adrenin is injected with an amount of amyl nitrite which is just capable of neutralizing its pressor effects, arterial disease identical with that produced by adrenin alone is manifested—in other words, adrenin produces its effects not because of its pressor tendency, but from some other much more subtle influence. "We have no experimental grounds for believing that persistence of any stimulus should at length lead to degeneration instead of hypertrophy of the middle coat."

Braun described the degenerative changes in the arteries in considerable detail, but Kaiserling does not attach much importance to the effects so far as the rabbit's aorta is concerned, because, he says, such changes sometimes occur in rabbits not treated with adrenin. Etienne and Parisot have come to the conclusion that elevation of the blood-pressure is not in itself sufficient to induce atheroma. This effect is of a toxic nature.

Klotz has recently made the important observation that, by periodic suspension of rabbits for a few minutes daily by the hind-legs most advanced aortic lesions can be induced, while Biedl and Braun record typical degenerative changes in the aorta and its branches, as a result of repeated compressions of short duration. The experiments which have been performed up to the present time do not enable us to decide what is the precise actual cause of the arterial changes after repeated injections of adrenin. There seems no reason why both the principal causes alleged—viz., a toxic action and a mechanical strain—should not both have a share in the production of the result.

2. *The Effects on other Structures, and the Mode and Seat of Action of Adrenin.*—Oliver and Schäfer investigated the effects of adrenal extracts on the *respiration* of the rabbit and the dog. Similar results were obtained in both, but the effect is most marked in the rabbit. It occurs soon after the administration of the drug, and may result in arrest of respiratory

movements for a short time. More commonly, however, there is produced a shallowing of the respirations, which persists for a certain period and then gradually passes off. In the dog no stoppage of respiration was ever obtained, but the respirations, although proceeding with an ordinary rhythm, were for a time slightly shallower. Other observers have also noted this effect of adrenal extracts upon the respiration. It is nearly always most marked with the first injection; with repeated injections the effect as a rule soon becomes trivial, and always becomes so if the injections are repeated a sufficient number of times. The subject has been recently investigated by Langlois and Garrelon. These authors seem to have obtained very considerable effects in the case of the dog; they report that if adrenalin be injected into a dog, expiratory apnœa sets in simultaneously with the beginning of the rise of blood-pressure. The duration of this apnœa is not constant. In most cases the respiratory movements begin again while the blood-pressure is still very high, and the respiration has most frequently returned to its regular type before the blood-pressure has returned to normal. If the injections are repeated in rapid succession, the influence disappears. After section of the vagi, the adrenalin injection has a much less marked action on the respiration. There is then a slowing of the movements, but no apnœa. Air rich in oxygen favours the occurrence of this apnœa, while an atmosphere with a large proportion of carbon dioxide hinders it.

Oliver and Schäfer discovered that adrenal extracts *prolong the curve of contraction of the skeletal muscles*, both in the frog and in the dog, though the period of latency is not increased. They were convinced that the curve is not a fatigue curve, but that it is comparable rather to the effect of a slight dose of veratrine. This effect has since been noted by many observers. Boruttau says that the phenomenon occurs in excised curarized muscle, and reminds one of the first stage of fatigue. Panella describes an anticuraric action of adrenin ("hemostasine") and states that it ("myosthenin," on this occasion) increases the activity of fatigued striated muscles. Cannon finds that the improvement of muscular contraction which apparently results from adrenal secretion (when the blood-pressure is controlled) is too slight to account for the increased muscular power observed during excitement. The main source of power

under these conditions is probably to be found in an immensely augmented activity of the nervous system. Fatigued muscles may however be prepared by secretion of adrenin for better responses to the demands of powerful nervous discharges. Adrenin improves muscular contraction by its specific effect on the muscle in eliminating fatigue and by improving the circulation through the muscle by means of its vaso-dilator action. Notwithstanding all this, it is difficult to demonstrate that there is in reality any beneficial effect of adrenin on voluntary muscular contraction.

Lewandowsky found that intravenous injection of adrenal extracts produces *dilatation of the pupil*, withdrawal of the nictitating membrane, protrusion of the eyeball, and slight opening of the eyelids. The last two symptoms are usually less marked than the action on the pupil and the nictitating membrane. The effects produced on the smooth muscle of the eye and the orbit are, in fact, the same as are called forth by stimulation of the cervical sympathetic. There is a short latent period, and the effects usually last some minutes, the period of duration being prolonged by cooling the animal. The action is peripheral, although local application to the eye is without effect. The experiments were performed upon cats. The same observer also recorded *excitation of the arrectores pili* and *inhibition of the bladder*.

Boruttau confirmed the observation as to the occurrence of dilatation of the pupil on intravenous injection of adrenal extract, and observed that in the cat subcutaneous injection produces no effect upon either the blood-pressure or the pupil. This writer further recorded that the injection causes *inhibition of intestinal movements*.

Lewandowsky pointed out that the extract is still effective after the superior cervical ganglion has been excised, and the nerve fibres proceeding from it allowed to degenerate. He concluded from this that the extract must stimulate the muscle substance directly, and not by means of the nerve endings.

Langley confirmed this observation of Lewandowsky, and agrees that the various eye effects are produced by a direct action of adrenal extract on the unstriated muscle. This author also found that the extract *excites the salivary and lachrymal glands, the liver, the muscular tissue of the uterus and vagina, of the vas deferens, the vesiculæ seminales, the dartos, and*

the muscular coat of the stomach. In the stomach inhibition of the muscular movements is produced. The effects on the movements of the intestine appear to differ according to the strength of the adrenin solution just as do the effects on the uterus and the pupil, and, as we have seen above, the effects on the blood-pressure. According to Langley, the effects produced by adrenal extract in the cat and rabbit may be arranged roughly in the following order as regards the amount of extract required per body weight to produce an obvious effect:

Rise of blood-pressure.

Inhibition of the sphincter of the stomach and of the intestine (rabbit).
Inhibition of the bladder.
Dilation of the pupil (cat).
Withdrawal of the nictitating membrane (cat)
Separation of the eyelids (cat)
} Slightly less readily than the foregoing.

Contraction of the uterus, vas deferens, seminal vesicles, etc. (rabbit).
Salivary and lachrymal secretion.
Inhibition of the stomach.
Inhibition of the gall-bladder and increased bile secretion.
Dilation of pupil (rabbit).
Inhibition of internal anal sphincter (rabbit).
Contraction of internal anal sphincter (cat)
Contraction of internal generative organs (cat)
} Effects relatively slight.

Contraction of the muscles of the hairs.

Contraction of tunica dartos of scrotum
Secretion of sweat
} No certain effect.

Langley divides the autonomic nervous system into sympathetic, cranial, sacral, and enteric, and points out that the effect of adrenal extract in no case corresponds to that which is produced by stimulation of a cranial autonomic or of a sacral autonomic nerve. On the other hand, *the effects produced are almost all such as are produced by stimulation by some one or other sympathetic nerve.* Notwithstanding this, he is inclined provisionally in his paper written in 1901 to favour the view that adrenin acts directly on muscle fibres and gland cells, but leaves unanswered the question as to why the action in the several cases should correspond so closely with that caused by stimulation of the sympathetic nerves.

Apocodeine abolishes the effects produced by sympathetic excitation, and was found by Dixon to abolish those produced by adrenin. He therefore concluded that adrenin acts upon

sympathetic nerve endings. It has been shown that in Mammalia, if the vagi have first been paralyzed with atropine, adrenal extract produces an augmented systole and acceleration of the heart. Both of these effects of adrenin may be abolished by the injection of large doses of apocodeine. Thus, Dixon found that in a cat $\frac{1}{2}$ c.c. of a 1 in 30,000 solution of adrenin increased the heart-rate from 92 to 211 per minute. After the injection of 100 milligrammes of apocodeine the same injection of adrenin now only increased the rate from 93 to 101 per minute. A further injection of 200 milligrammes of apocodeine was then administered, and caused the rate of the heart to diminish to 87 per minute. Adrenin now, even in large doses, produced no acceleration, and there was no augmentation of the systole. Dixon therefore concludes that the whole effect of adrenal extract on the heart is a stimulation of the sympathetic nerve endings. Similarly, the vasomotor nerve endings are paralyzed by apocodeine, and after the administration of this drug no vasoconstriction can be induced by means of adrenin.

The addition of adrenin to any of the ordinary perfusion fluids enables the heart to maintain its activity over much longer periods of time. The time may be quadrupled by such addition (Burridge).

This view, that adrenin acts on nerve endings, is supported by the observations of Macfie, who found that extracts of the adrenal and other tissues are without effect upon the embryonic heart, upon leucocytes, and upon cilia. Again, the work of Brodie and Dixon, who find that there are no vasomotor nerves for the pulmonary arterioles, and that adrenin, when perfused through the pulmonary vessels, produces no constriction, is decidedly in favour of the theory that the substance acts upon nerve tissue only.

On the other hand, Boruttau considers that the action is direct on somatic muscle, since it occurs in curarized muscle,[1] and, according to Lewandowsky, the dilation of the pupil and other eye effects are produced by a direct action of adrenal extract on the constricted muscle. This was inferred from the fact, referred to above (p. 179), that the extract is still effective

[1] It does not follow, of course, that, because a curarized muscle cannot be excited through its nerve, therefore the *whole* of the nerve endings are paralyzed.

after the superior cervical ganglion has been excised and the nerve fibres from it have degenerated. With regard to somatic muscle, Langley is inclined to accept Lewandowsky's view, while in the matter of plain muscle he is content (in the paper of 1901-02) with the generalization that the effect of adrenin is the same as the effect of exciting the sympathetic nerves supplying the particular tissue.

In studies on the action of adrenin on the bloodvessels of the rabbit's ear Meltzer and Auer showed that section of the sympathetic has a marked effect on the results of intravenous injection of the drug. While on the normal side the constriction of the vessels reaches its maximum in a few seconds, on the side of the section it lasts a very long time, and is very pronounced. Following up the discovery of Lewandowsky (confirmed by Boruttau and Langley), that intravenous injection of adrenin induces a temporary dilation of the pupil, Meltzer and Auer found that, though subcutaneous injection and conjunctival instillation produce no effect in the normal animal or after section of the cervical sympathetic, yet such administration produces very striking dilation of the pupil after removal of the superior cervical ganglion—that is to say, "the paradoxical effect" is marked in the case of adrenal extract.[1]

These observations were confirmed and extended by Elliott, who generalized as follows: "This, then, is true for all the muscles thrown into contraction by adrenalin, that after decentralization—*i.e.*, degenerative section of the preganglionic sympathetic nerves—and still more clearly after denervation (degenerative section of the post-ganglionic sympathetic nerves), they contract in the presence of adrenalin alike with greater irritability and persistence." Elliott concluded as to the localization of the action of adrenin that the excitation must be due to some substance within the muscle fibres being affected by the drug, and suggested that this substance is present at the "myoneural junction," where it is originally formed.

[1] Meltzer and Auer point out an important difference between mammals (rabbits and cats) and the frog. In the latter animal in a normal state, subcutaneous injection or instillation into the conjunctival sac produces in a few minutes a characteristic dilation of the pupil, which may last for hours, so that the frog has become a convenient means of testing adrenal extracts.

Schäfer adds a further suggestion—viz., that the formation of this substance, being once started, its amount is also controlled by the sympathetic, and if this control be cut off an inordinate quantity may accumulate, thus increasing the excitability of the isolated muscle fibres. The observations of Macfie (see above, p. 181) prove that the presence of nerve fibres is essential to the original appearance of such hypothetical excitable substance.

These different views do not accord very well together, but the fact that adrenin has functionally a very intimate relation to the sympathetic nervous system is particularly interesting when we remember the accepted origin of the chromaphil tissues.

According to recent observations by Langley, in all cells two constituents at least must be distinguished: (1) Substances concerned with carrying out the chief functions of the cells, such as contraction, secretion, the formation of special metabolic products; and (2) receptive substances, especially liable to change, and capable of setting the chief substance in action. According to this author, the active substance of the adrenals produces its effects by combining with the receptive substance, and not on nerve endings nor the chief substance. So that in this view the controversy as to whether adrenin acts on muscle itself or on sympathetic nerve endings is compromised by assuming that there is some material in cells originally under control of the sympathetic, which material is specially excited by adrenin.

This theory of Langley has not, however, been universally accepted. There is some evidence which tends to show that after all adrenin acts directly upon the smooth muscle.

Among the other effects of adrenin which have been noted are increase of intra-ocular pressure after intravenous injection, and changes in the structure and function of the kidneys. Bardier and Fränkel record a diminution of secretion of urine owing to constriction of renal vessels after the administration of adrenin. Subsequently and more significantly the conditions are reversed. Adrenin mydriasis has been employed as a diagnostic sign of increased diffusibility of the cornea. Adrenin appears to increase the activity of anæsthetics applied locally to a nerve. It is said that adrenin gives rise to increased flow from the thoracic duct as long as the blood-pressure is high.

It has been stated recently that rhythmic contractions of arteries occur normally in the rabbit's ear and that adrenin augments these contractions.

There seems to be considerable difference of opinion as to the effect of adrenin on the secretion of sweat.

Redfield suggests that the melanophores of the amphibia are controlled by adrenin in the circulation.

Cats appear to be peculiarly liable to collapse after intravenous injection of adrenin under light chloroform anæsthesia. Full chloroform anæsthesia appears to be absolutely protective. There is probably some unknown condition of the heart under the influence of low percentages of chloroform, which renders it incapable of accommodation to vascular strain.

In the experience of the present writer, also, it has very frequently happened that dogs have been killed by a dose of adrenin (administered intravenously) which it was expected would only be sufficient to produce a moderate rise of blood-pressure. This has occurred with both adrenal extracts and the purified adrenin, and it is not clear that it is dependent on the nature or amount of the anæsthetic employed. The phenomenon seems to depend upon a peculiar idiosyncrasy in some animals, and is comparable to what was found in respect of the general effects produced in various animals by subcutaneous injections (see p. 159).

A large amount of work has been carried out upon the antagonism between adrenin and various other drugs. In many respects there appears to be a true antagonistic action between adrenin and calcium chloride, although the latter substance does not hinder the production of adrenin arteriosclerosis. Adrenin is also stated to act as an antidote to poisoning by strychnine, aconitine, and belladonna. A pharmacological antagonism is alleged between adrenin and secretin, while adrenin exercises no action which can be regarded as antagonistic to that of albumoses and of pilocarpine upon the pancreatic and salivary secretions. It is stated that the chlorides of calcium, barium, magnesium, and potassium can neutralize the mydriatic action of adrenin.

The table on pp. 187–191, taken from Biedl, gives a summary of the chief actions of adrenin and a comparison between these actions and those produced by stimulation of nerves belonging to the sympathetic and autonomic systems.

Notwithstanding the almost universal acceptance of the view that the action of adrenin is identical and co-terminous with that of sympathetic nervous action, it is well to bear in mind that the evidence is in some directions contradictory and in others rather meagre. As will be seen from the table it is by no means easy to formulate an absolute parallelism in every instance, and the difficulty becomes still greater if we take into consideration the different effects of varying doses of adrenin. The parallel problem as to the effects of varying degrees of stimulation upon the sympathetic fibres does not seem to have been worked out.

M. The Chemical Nature of the Active Substance of the Adrenal Medulla and other Chromaphil Tissues

It is one of the greatest triumphs of physiological chemistry that within seven years of the discovery of the powerful effects of extracts of the adrenal medulla, the active principle was obtained in crystalline form, and that five years later its composition has been so completely ascertained that it has been synthesized, and the pure active synthetic product can now be obtained from the manufacturing chemists.

In 1856 Vulpian described a powerfully reducing substance in the medulla of the adrenal body. This material was found to give various colour reactions on being oxidized—*e.g.*, with ferric chloride it gave a dark green or blue colour, and with chlorine, bromine, or iodine water or caustic alkalies a rose red. Several authors attempted, but without success, to isolate the "chromogen" of the gland from a lead precipitate. They all obtained decomposition products. Krukenberg, however, established the important fact that the adrenal chromogen, in regard to certain properties (iron reaction, reducing power, production of a dark coloration with oxidizing agents), corresponds with pyrocatechin.

Immediately after the publication of the discovery of the pressor action of adrenal extracts, Moore concluded that the active substance is identical with the chromogen described by Vulpian.

Fränkel, by treatment of adrenal extracts with alcohol, acetone, and ether, obtained a syrupy preparation of great physiological activity. This was the first claimant to the

title of the isolated active principle of the medulla of the adrenal body. It was called "*Sphygmogenin.*" [1] Fränkel was also able to show that the chromogen furnishes a benzoyl product insoluble in water, and contains nitrogen in stable combination. This author was the first to express the opinion that the pressor substance is a nitrogenous derivative of orthodihydroxy-benzene. The statement that from it pyrocatechin could be obtained simply by boiling with hydrochloric acid was easily refuted. V. Fürth, on the other hand, showed that by dry distillation of the chromogen a compound is obtained which, as regards its reaction towards iron salts (emerald green coloration, which on the addition of alkali becomes carmine red) and its solubility (in ether, whether out of acid or alkaline solution), corresponds with pyrocatechin.

With a view to the isolation of the extraordinarily unstable and easily oxidizable active substance, v. Fürth extracted with alcohol at a low temperature ; then, after getting rid of inactive substances by means of neutral lead acetate, threw down a precipitate with ammoniacal lead hydroxide. By decomposing with sulphuric acid, concentrating the filtrate *in vacuo* and in a stream of carbonic acid gas, extraction of the residue with alcohol, and precipitation with ether, the chromogen was obtained in the form of a slightly pigmented precipitate which was extremely active physiologically.

Turning to account an observation by Hofmeister that by reduction of the adrenal extract with zinc dust in acid solution one could counteract to a certain extent the instability of the chromogen, v. Fürth made use of the following improved process : The adrenals were extracted with dilute zinc sulphate solution, the extracts freed from protein by heating, and treated with excess of ammonia, by which means the chromogen was thrown down as a zinc compound. This was washed, decomposed in a mixture of alcohol and sulphuric acid, the acid filtrate decolorized by means of heating with zinc dust, neutralized with zinc oxide, filtered hot, freed from zinc salts by means of alcohol and ether, and finally concentrated. The process was also varied by using ammoniacal lead hydroxide instead of the zinc compound. The amorphous pyrocatechin-

[1] No chemical criteria of the purity of this substance were given. Fränkel did not show that it possessed a constant percentage composition, and no attempt was made to establish even an empirical formula for it.

TABLE OF ACTIONS OF ADRENIN COMPARED WITH THOSE OF STIMULATION OF THE SYMPATHETIC AND THE AUTONOMIC NERVES (BIEDL)

Organs and Tissues.	Action of Adrenin.	Sympathetic Thoracico-Lumbar Nerves.	Effect of Stimulation of the— Autonomic Cranial Nerves.	Autonomic Sacral Nerves.	
SMOOTH MUSCLE:					
Alimentary canal: Œsophagus.	Relaxation	Relaxation	Contraction		
Cardiac sphincter	Relaxation	Relaxation . .	Contraction and relaxation (*Langley*)		
Stomach: Cat, rabbit . .	Inhibition	Inhibition . .	First inhibition, then powerful contraction (*Langley*)		
Birds	Inhibition	Inhibition			
Frog	Contraction	Contraction	(?)		
Gall-bladder	Relaxation	Relaxation . .	Contraction and relaxation (*Bainbridge* and *Dale*)		s
Bile-duct	Contraction	Contraction			
Small intestine: Mammals .	Inhibition	Inhibition	Contraction and inhibition (*Bayliss* and *Starling*)		
Birds	Contraction	Contraction	(?)		
Ileo-cæcal sphincter (cat) .	Contraction	Contraction	No action		
Colon and rectum . . .	Relaxation	Relaxation		Contraction of end portion (birds)	
Recto-coccygeus muscle . .	Relaxation	Relaxation		Contraction	
Internal anal sphincter: Rabbit	Relaxation	Relaxation		Rapid relaxation	
Dog and cat	Contraction	Contraction		Variable	Pelvic nerve.
Birds	Contraction	Contraction		(?)	
Urinary apparatus: Ureter .	Contraction	Contraction		Relaxation (?)	
Urinary bladder: Cat and monkey	Relaxation	Relaxation		Contraction	
Dog and rabbit	Indifferent	Indifferent		Contraction	
Ferret and goat . . .	Contraction	Contraction		Relaxation	
Frog	Contraction	Contraction			
Urethra	Contraction (?)	Contraction (?)		Relaxation (?)	

TABLE OF ACTIONS OF ADRENIN COMPARED WITH THOSE OF STIMULATION OF THE SYMPATHETIC AND THE AUTONOMIC NERVES (BIEDL)—*Continued*

Organs and Tissues.	Action of Adrenin.	Effect of Stimulation of the— Sympathetic Thoracico-Lumbar Nerves.	Autonomic Cranial Nerves.	Autonomic Sacral Nerves.
Genital apparatus :				
Uterus, Fallopian tubes, vagina : Virgin	Contraction	Relaxation and contraction		
Pregnant	Powerful contraction	Powerful contraction		
Ves. seminales, vasa deferentia	Contraction	Contraction		
External genitals :				
Retractor penis muscle	Contraction	Contraction		Relaxation (*Langley*).
Ano-genital muscles	Contraction	Contraction (stronger)		Relaxation (pelvic nerve).
Tunica dartos (*Lieben*)	Relaxation	Contraction		
Lungs : Bronchial muscles	No action (relaxation ?)	No action	Contraction (vagus)	
Skin : Arrectores pilorum :				
Mammals	Weak contraction	Stronger contraction		
Birds	Contraction	Contraction		
Eyes : Retractor palpebr. tert.	Contraction	Contraction	Inhibition (abducens nerve) (*Löwi* and *Fröhlich*)	
Lid muscles	Contraction (opening of lid-cleft)	Contraction		
Orbital muscle	Contraction (protrusion of the eyeball)	Contraction		

Pupil : Sphincter iridis		Contraction (oculomotor and ciliary nerves)		
Dilatator	After elimination of sympathetic inhibition, powerful contraction	(Inhibition) and contraction		
Ciliary muscle			Contraction (ciliary nerves)	
Pigment cells : Skin (*Lieben*)	Contraction	Contraction (*Gaup*)		
Retina (*Klett*)	Contraction			
HEART :				
Auricles	Beat accelerated and strengthened	Beat accelerated and strengthened	Inhibition (vagus)	
Ventricles : Mammals	Beat strengthened	Beat strengthened		
Birds (*Elliott*)	No action	No action (*Gaskell*)	No inhibition	
Reptiles (tortoise, *Elliott*)				
Amphibians	Beat strengthened			
Fishes (selachians, *Biedl*)	Beat strengthened			
Invertebrates (crab, *Elliott*)	No action			
Coronary vessels	Dilatation	Dilatation	Constriction (?) (vagus)	
Isolated strips (*Langendorff*)	Relaxation			
BLOODVESSELS :				
Of the brain (*Biedl* and *Reiner*)	Direct action Constriction	Constriction	Dilatation (?) (vagus)	
Of the retina (*Kahn*)	On intravenous injection, passive dilatation			
Of buccal mucous membrane	Constriction (*Elliott*)	Dilatation (*Dastre* and *Morat*)	Constriction (lingual nerve (*Löwi* and *Fröhlich*)	

TABLE OF ACTIONS OF ADRENIN COMPARED WITH THOSE OF STIMULATION OF THE SYMPATHETIC AND THE AUTONOMIC NERVES (BIEDL)—*Continued*

Organs and Tissues.	Action of Adrenin.	Effect of Stimulation of the— Sympathetic Thoracico-Lumbar Nerves.	Autonomic Cranial Nerves.	Autonomic Sacral Nerves.
Of lingual mucous membrane and of the salivary glands	Constriction	Constriction	Constriction and dilatation	
Of the lungs	No certain action	No certain action		
Of abdominal viscera:				
Spleen	Constriction	Constriction		
Small intestine				
Rectum				Dilatation (pelvic nerve)
Kidney	Elective constriction (*Jonescu*)	Constriction		
Internal genital organs	Constriction	Constriction		
External genital organs (vessels of penis)				Dilatation (pelvic nerve = *Nervus erigens*)
Of the skin and the muscles	Direct action; constriction; intravenous injection; passive dilatation	Constriction		
GLANDS:				
Lachrymal glands	Secretion	Secretion		
Mucous glands: Mouth, œsophagus	Secretion	Secretion		
Salivary glands	Secretion (sympathetic saliva)	Secretion (sympathetic saliva)	Secretion chorda tympani) (chorda saliva)	

Gastric glands	Secretion (?) (*Yukawa*)		Secretion (vagus)	
Liver	Scanty bile secretion	Bile secretion		
Pancreas	Increased secretion	Secretion	Secretion (vagus)	
Adrenal bodies	Vasoconstriction and vasodilatation	Secretion (vasodilatation, *Biedl, Waterman* and *Smit*)		
Kidneys	Primary inhibition, then increased secretion (*Bardier* and *Fränkel*)			
Sweat glands	No secretion	Secretion		
Glands of skin and nictitating membrane of frog	Secretion	Secretion		
Formation of lymph	Increased (œdema), increased flow from thoracic duct (*Camus*)			
Resorption	Slowed			
METABOLISM:				
Sugar tonus	Raised (glycosuria)	Raised (glycosuria), diabetic puncture		
Heat tonus	Raised	Raised, heat puncture		

like substance obtained by these methods was precipitable from alcoholic solution by means of ether. In the state of solution preserved in sealed tubes it showed considerable stability, and possessed a high degree of physiological activity. A dose of 0·000025 gramme raised the blood-pressure of a rabbit to nearly double its original height. At a later date Abel made a comparison between a preparation obtained by the above lead process and the crystalline *adrenalin* obtained by Takamine's process (*vide infra*). The test was a double one. On the one hand a colorimetric estimation of the iron compound was made, and on the other hand the relative effect upon the blood-pressure was noted, and in neither case was v. Fürth's substance shown to be weaker than that of Takamine.[1] Von Fürth called his substance "*Suprarenin*."

Abel and Crawford converted the pyrocatechin-like substance into a benzoyl compound, and observed after saponification by addition of alkali a smell like that of coniine or pyridine. Furthermore, they made the very important observation that, by distillation of the product with zinc dust in a stream of hydrogen, pyrrol was obtained, and they arrived finally at the conclusion that the active principle of the adrenal medulla belongs to the series of the pyridine bases. This has not been confirmed by subsequent investigation. Moore came to the same conclusion, since he observed that if some adrenal extract be cautiously fused with caustic potash so as to avoid charring, the peculiar odour of pyridine was at once obtained. But, as pointed out by Moore in this relation, it is piperidine, and not pyridine, which has a marked effect upon the blood-pressure. Moore surmised, therefore, that the active substance is a piperidine derivative—*i.e.*, that it contains a hydrogenated ring.

V. Fürth next proceeded to the formation of an iron compound of the active principle. An extract of the glands was made by boiling with acidulated water with the addition of zinc dust. The extract was concentrated *in vacuo*, the residue extracted with methyl alcohol, and the solution, after getting rid of inactive substances by means of zinc chloride and acetone, decomposed with chloride of iron and ammonia. The iron compound of the "suprarenin" separated out in the form of a carmine-red flocculent precipitate. The substance was then

[1] In recognition of this fact the term "suprarenin" is still frequently used, especially in Germany, for the active principle of the chromaphil tissues.

repeatedly dissolved in dilute ammonia, and precipitated by means of acetone, and the final product was extremely active physiologically, though not yet chemically pure. Analysis indicated that the suprarenin probably contained C 8–9, H 11–13, O 3–4 per cent.

Abel came to essentially different conclusions as to the chemical nature of the active substance. This worker benzoated adrenal extracts, saponified the purified benzoyl product in the autoclave at a pressure of 3 to 5 atmospheres with dilute sulphuric acid, and precipitated with dilute ammonia or picric acid from the solution so obtained a substance which he called "*Epinephrin*," which he considered was the isolated active principle of the adrenal medulla. It yields picrates and other salts, and is a substance of an alkaloidal nature, having the elementary composition $C_{17}H_{15}NO_4$. V. Fürth has shown that Abel's epinephrin is quite a different substance from his own suprarenin, that the former possesses in itself no physiological action, and that whatever physiological effects may be induced by its administration are due to admixture with suprarenin. Epinephrin is also distinguished from suprarenin by its precipitation by means of precipitants of alkaloids (phosphotungstic acid, picric acid, tannic acid, etc.), by zinc chloride, by the absence of reducing power, and the absence of the colour reaction with perchloride of iron. Its separation from suprarenin can conveniently be effected by careful neutralization of the acid solution with very dilute ammonia, by which means the epinephrin separates out as a dark flocculent precipitate easily soluble in excess of ammonia.

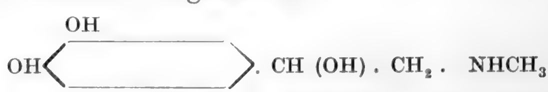
Abel has since shown that epinephrin is to be looked upon as a derivative of suprarenin arising as a result of the treatment with acid in the autoclave. The fact that a methylindol is obtained by fusing epinephrin with potash must be regarded as of importance in explaining the constitution of suprarenin. Abel has suggested the possibility that by the autoclave treatment a portion of the nitrogen is split off from the suprarenin molecule. This view has been confirmed by v. Fürth. Afterwards, however, Abel was inclined to believe that by treatment of the benzoyl product in the autoclave saponification was not complete, and the resulting substance was still a benzoyl product ($C_{17}H_{15}NO_4$); epinephrin would therefore

be a monobenzoyl-suprarenin $(C_6H_5CO)\ C_{10}H_{10}NO_3$; to suprarenin itself must then be allotted the formula $C_{10}H_{11}NO_3$.

The next important step was the production of the active substance in a crystalline form. This was effected by Takamine and Aldrich independently. The method in both cases was the same. Very concentrated adrenal extracts were largely freed from inactive substances by treatment with alcohol, lead acetate, etc.; then the active substance was precipitated in the form of microscopic crystals by the addition of concentrated ammonia. The precipitate was then purified by repeatedly dissolving in acid and reprecipitating with ammonia. The resulting prismatic needles or rhombic plates were those of the purified and isolated active principle—adrenalin.

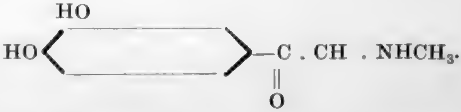
According to v. Fürth, a careful comparison of the composition and physiological action of adrenalin with those of his suprarenin indicates that they are one and the same substance. He has decomposed the "suprarenin" iron compound with sulphuric acid and thereby obtained "adrenalin" in crystalline form.

All the authors quoted have obtained different analytical results and suggested different formulæ. Aldrich suggested from his analyses the formula $C_9H_{13}NO_3$, Takamine $C_{10}H_{15}NO_3$, and Abel $C_{10}H_{13}NO_3 + \frac{1}{2}H_2O$. The empirical formula of Aldrich is now generally accepted, and from the combined researches of v. Fürth, Jowett and Pauly, the constitutional formula is regarded as—



That is to say, adrenalin is therefore ortho-dioxyphenyl-ethanol-methylamine and is related to tyrosin—*p*-oxyphenyl-amino-proprionic acid.

If adrenalin be oxidized, we get a substance having the formula:



This substance, *adrenalon* (methyl-aminoacetylpyrocatechin) has been prepared synthetically by Friedmann, Stolz, and

Dakin. The reduction product appears to be chemically identical with adrenalin in all respects except that it is optically inactive, while the natural body from the adrenal medulla is lævorotatory ($^aD = 43^o$) according to Pauly.

On testing the physiological action of the synthetic (racemic) adrenalin and comparing it with that of the natural adrenalin, Cushny found that the latter acts twice as strongly on the blood-pressure as the former. From this he inferred that dextro-adrenalin is devoid of any physiological activity. Adrenalin thus proves analogous to hyoscyamine and hyoscine, in which the dextrorotatory form is almost devoid of the specific action of the natural lævorotatory alkaloid on the peripheral tissues.

Flächer recently succeeded in dividing the racemic suprarenin or adrenalin into its two optically active components. These have been subjected to a pharmacological examination by Cushny. The synthetic *l*-adrenalin was first compared with natural adrenalin isolated from the glands, and was found to be identical with it in its power of raising the blood-pressure. The *d*-adrenalin was next compared with these and found to possess one-twelfth to one-fifteenth of their action—that is, twelve to fifteen times as much of *d*-adrenalin was required to raise the blood-pressure to a definite degree. The earlier statement of Cushny that the lævorotatory alkaloid is twice as strong as the racemic is thus seen to be practically correct, these later experiments showing that a closer approximation would put the relative strengths between 24 : 13 and 30 : 16. Cushny found further that the doses necessary to cause glycosuria are similarly in the proportion of 12 to 18 : 1. The minimal lethal doses as tested by subcutaneous injection appear to bear the same relation. No evidence was obtained suggesting that adrenalin acts elsewhere than on the receptive substances of the sympathetic myoneural junction.

We have seen that the terms "epinephrin," "sphygmogenin," "suprarenin," and "adrenalin" have been applied to the active principle of the chromaphil tissues. Other names which have been employed are "hemisin," "paraganglin," and "myosthenin." Adrenalin is, however, the term most commonly used; but it is advisable to adopt a name which has no commercial attachments, and Schäfer suggests "adrenin." This term has been adopted in the present work,

and is used where reference is not made to some particular preparation.

In the laboratory adrenin may perhaps be prepared most conveniently by Abel's method, that is to say, by extracting chromaphil tissues with 3·5 per cent. trichloracetic acid in alcohol, filtering, and adding ammonia. Adrenin is precipitated, filtered off, and washed with water, ether, and alcohol. A yield of about 2 per cent. is obtained. A further 1 per cent. can be obtained by extracting the mass a second time with trichloracetic acid. It is recrystallized by dissolving in alcohol with acetic acid and precipitated by ammonia.

Nagai gives the following method for the synthesis of adrenin: (1) Diacetyl-protocatechuic aldehyde prepared by the reaction of AcCl or Ac_2O on protocatechuic aldehyde is condensed with nitromethane in the presence of weak inorganic or organic bases; (2) the resulting diacetyl-dihydroxy phenyl-initroethanol is reduced in the presence of HCHO by means of Zn dust and HOAc; (3) the diacetyl-adrenalin so formed is hydrolyzed by HCl, given adrenalin hydrochloride.

It is a colourless crystalline substance, having a melting point of 211–212° C. It is not easily soluble in cold water, but more readily in hot. It is insoluble in most organic solvents such as alcohol, ether, or chloroform. It is a strong base and is soluble in mineral acids and caustic alkalies, while it is insoluble in carbonates or ammonia. It is not precipitated by alkaloidal reagents like picric acid, tannic acid, sublimate, phospho-tungstic acid, etc. As a phenol it forms water-soluble compounds with fixed caustic alkalies.

Commercial solution of adrenin chloride is the usual starting-point in making prescriptions. This solution contains one part in a thousand of adrenin chloride dissolved in normal saline solution with about 0·5 per cent. of chloretone. The solution keeps fairly well if air be excluded.

As it will be more fully stated below (p. 204), adrenin is widely employed as a drug, and numerous preparations have been placed upon the market, and manufacturing druggists have extensively advertised many forms of the pure product. As pointed out by Schultz, the different preparations vary greatly in physiological activity—some, even, being worthless, this being due partly to a lack of care in the process of preparation, and partly to the nature of the container and solvent

used in bottling the extract. Schultz narrates that in one instance only 6 grammes of pure adrenalin could be obtained from a sample supposed to contain 19·4 grammes of natural *l*-adrenalin base. He finds that the ratio of physiological activity of the natural *l*-base and the synthetic *dl*-product are to each other as 2 : 3 instead of 1 : 2, according to Cushny.

The physiological activity of all adrenin-like bodies can be assayed by the blood-pressure method and their efficiency expressed in terms of pure adrenin base. Hence, if one has two solutions, a known adrenin solution, 1 c.c. of which contains *a* grammes of the base, and an unknown containing a certain amount, *y*, of vasoconstrictor exciting substance, they can readily be checked against each other by the blood-pressure method. Whichever solution is the stronger can be diluted until 1 c.c. injections of it cause the same rise of blood-pressure as the other, and finally their relative activity calculated by the following equation :

$$\frac{a \text{ adrenin base}}{y \text{ vasoconstrictor excitant}} = \text{relative activity.}$$

Folin, Cannon, and Denis have described a colorimetric method for the determination of adrenin. Folin and Denis had previously described a phospho-tungstic acid reagent which gives a blue colour with uric acid, and also with poly-phenol compounds. The method applied to adrenin in solution reveals the presence of one part of adrenin in three millions of water. Using a solution of uric acid of known strength for the colour standard and accepting the proved observation that adrenin has thrice the chromophoric value of uric acid, it requires but a few minutes to assay a solution of adrenin.

Schultz has investigated a series of specimens of adrenin sold under different names by various firms. Of the seven different brands of "epinephrin" examined, only three possessed an activity that equalled the standard. The other solutions varied from 3·75 to 71 per cent. of the required activity. Some of the solutions were worthless, and perhaps even dangerous. Certain solutions, though showing a high degree of activity upon opening the original package, quickly deteriorated in spite of the extra precautions taken to guard against conditions known to further this process. This author remarks that, on the other hand, some of the preparations now upon the market are of the very highest quality.

It has recently been shown that the iodine reaction, the mercuric chloride reaction, and the bi-iodate reaction are due wholly or in part to oxidation. Potassium persulphate was found by Ewins to have a similar oxidizing action upon adrenin, giving a characteristic red colour. This reaction is stated to have advantages over those mentioned above both in sensitiveness and in being readily obtained with crude extracts of chromaphil tissues. The mercuric chloride reaction appears to be due to the oxidation of adrenin by such oxidizing agents as mercuric chloride, silver nitrate, or platinic chloride under the catalytic influence of salts of metals with "weak" acids (*i.e.*, salts which are hydrolytically dissociated by water). The reaction may be compared with the results which have been obtained in the investigation of certain "laccases." The characteristic colour reactions of adrenin are given by certain other closely related bases—namely, by (*a*) the amino base, corresponding to adrenin; (*b*) dihydroxyphenylethylamine and the corresponding methyl, ethyl, and propylamino bases; (*c*) amino-aceto pyrogallol. The bases of the type amino-aceto catechol do not give these reactions (Ewins).

The physiological action of adrenin, an action simulating that of the true sympathetic nervous system, is possessed also by a large series of amines, the simplest being primary fatty amines. Barger and Dale describe all such amines and their action as "sympathomimetic." They find, as the result of a careful investigation, that the more nearly the structure of an amine approaches to that of adrenin, the more intense and the more specific is its sympathomimetic action. All the chemical products which possess this specific action are primary and secondary amines. The quaternary amines corresponding to the aromatic members of the series have an action closely similar to that of nicotine. There are two optimum conditions of chemical structure in which the action is most pronounced. The first is a benzene ring with a side-chain of two carbon atoms, the terminal one bearing the amino group. The second is the presence of two phenolic hydroxyls in the 3 : 4 position relative to the side-chain; when these are present an alcoholic hydroxyl still further intensifies the activity. A phenolic hydroxyl in the 1 position does not increase the activity.

As a practical result of these investigations 3 : 4 dihydroxyphenylethylmethylamine, one of the most active of the sympa-

thomimetic amines, has been put upon the market and is advertised under the name of "epinine" ("the synthetic hæmostatic"). It is claimed that this product "possesses the characteristic physiological action of the extract of the supra-renal gland, but is superior in that its purity is chemically controlled, its stability is greater, and the rise of blood-pressure it produces is more prolonged." According to Burridge, epinine is capable of altering the reaction of the heart to calcium salts in a solution perfusing that organ. When the substance is acting the heart can remain active on a solution of much lower calcium content than before. If the heart be perfused with a solution of such low calcium content that the beats cannot be recorded, the addition of traces of epinine to the perfusing fluid causes long-continued good contractions. Epinine can restart beating in hearts inhibited by potassium salts. Larger doses render the heart less susceptible to certain actions of calcium.

There are now on the market several other substitutes for adrenin.

As bearing on the general question of the functions of adrenin throughout the animal kingdom, attention must be called to the discovery by Abel and Macht of adrenin in the poison glands of a tropical toad (*Bufo agua*). The adrenin-producing acini are limited to the glandular masses behind the eye and surrounding the tympanum, known as the "parotoid" glands, the chromaphil reaction being negative in all other cutaneous glands. But in these glands there is no true chromaphil tissue. The cells themselves do not react to potassium bichromate, nor does the poison-sac contain chromaphil material until long after the disappearance of all epithelial elements. The adrenin is probably the result of a change produced in a mother substance which is very likely an amino-acid. Wiechowski could not find adrenin in the glands of the Bohemian toad, though he describes the secretion as chromaphil, that is to say, it is stained brown by salts of chromic acid. Examples of tissues which give the chromaphil reaction and yet do not contain adrenin are gradually accumulating.

In *Bufo agua* we have an example of the *external* secretion of adrenin. It is not clear what effect the adrenin has upon the poisonous activity of the other important ingredient

("Bufagin") in the venom. The crude poison of the toad contains nearly 7 per cent. of adrenin.

N. The Origin of Adrenin in the Body

Nothing is definitely known of the nature of the parent substance from which adrenin is derived. It has been supposed that the waste products of muscular metabolism are converted into adrenin. This view appears to be based upon results obtained by Boruttau and Langlois upon frogs whose adrenal bodies had been removed, and which were benefited by injection of adrenal extracts. The theory would imply the formation of adrenin from some such substance as creatin. This is the least probable of the three suggestions.

Abelous, Soulié, and Toujan are of the opinion that adrenin is manufactured in the cortex from tryptophane.

Halle has suggested that one of the substances from which adrenin is formed in the organism may be tyrosin, and has brought forward some evidence for this view. He points out that adrenin might be produced from tyrosin by (1) introduction of a hydroxyl group into the benzene ring; (2) elimination of CO_2 from an amino-acid to form an amine; (3) the methylation of nitrogen; (4) the introduction of a hydroxyl group into an aliphatic chain. He states that when two portions of emulsion of fresh ox or pig adrenal were taken, to one of them tyrosin being added, both being kept under aseptic conditions for six days in an incubator, the sample containing the tyrosin was found to have from 14 to 33 per cent. more adrenin than the control.

Gessard imagines a relationship between tyrosin and adrenin, because both substances become pigmented in a similar manner by the action of tyrosinase.

The theoretical speculations of Halle would appear to be open to criticism. as pointed out by Ewins and Laidlaw. Moreover, the last-named observers were unable to confirm Halle's experimental results. The matter is by no means settled, and, although the hypothesis that adrenin may be derived from tyrosin is not supported by the evidence before us, yet it would be rash to dismiss this substance from consideration as one of the possible precursors of adrenin in the animal economy.

O. The Mode of Disposal of Adrenin in the Body

It was found by Oliver and Schäfer that adrenal extracts not only produce a contraction or increase of tone in cardiac and vascular muscle, but that frogs which had received a subcutaneous injection show an increased power of contraction of the skeletal muscles on stimulation of their nerves. This also applies to mammals, and the effect lasts for some time after the effects upon the vascular system have disappeared. It was therefore concluded that the active substance is probably taken up by, and remains for a time stored within, muscle, and that this may in a measure account for its disappearance from the blood. It is not excreted by the urine, nor is it at once reabsorbed by the capsules. Its ultimate disappearance is probably due to a process of oxidation in the tissues. Oxidation of the active principle does not occur in the blood.

Langlois found that the rate of destruction is proportional to the activity of the tissues generally. Thus, in hibernating or cooled animals, the process of destruction is slow. According to the author, destruction of the active principle occurs throughout the whole body, though chiefly in the liver. The injection into the mesenteric vein of a dose sufficient to raise the blood-pressure considerably, if injected into the general circulation, produces no effect. Athanasiu and Langlois also found that Fränkel's "sphygmogenin," when injected, is destroyed in the liver. It was also stated that adrenal extracts are rendered inactive by ozone or other oxidizing agents.

The experiments of Embden and v. Fürth show that digestion of adrenin for two hours with normal blood, laky blood, or blood-serum, causes a considerable destruction of the active principle. On the other hand, addition of muscle, liver, or lung extract to the blood (as also perfusion experiments) causes a less destruction or none at all. Comparative experiments with weak alkaline solutions teach that the destruction in the blood is essentially due to the alkali, and the hindrance to destruction in the organs to the formation of acid. Nevertheless, these authors are not of opinion that the rapid cessation of action on the vessels is to be attributed to a rapid oxidation; they consider, rather, that the contraction of the muscles of

the bloodvessels ceases so soon as the concentration of the adrenal solution by diffusion or dilution with the blood and tissue fluids sinks to a certain level.

The disappearance of the effect of a dose of adrenin has been attributed to the alkalinity of the blood. Thus, Kretschmer finds that if this is diminished by the administration of acids, the effect of the drug upon the blood-pressure is prolonged. It is even affirmed that the active substance does not disappear from the blood, and that the blood of a rabbit which has received a dose of adrenin will cause the typical rise of blood-pressure if injected into another rabbit, although the effects upon the first animal may have disappeared.

The subject of the inactivation of adrenalin and one of the sympathomimetic amines *in vitro* and *in vivo* has recently been investigated by Cramer, who reports that a solution of adrenalin can be completely inactivated by allowing it to stand with a dilute solution of formaldehyde for a few minutes. "Epinine" (see p. 199), under similar circumstances, also becomes inactivated. Pituitrin and the other hormones are not so inactivated by formaldehyde. It is suggested that the inactivation of adrenin in the organism is brought about not by a process of oxidation, but by a combination with a product of metabolism produced by the cells on which adrenalin has acted, and that it is a process similar to the reaction *in vitro* previously described.[1]

P. The Proteins, Lipoids, etc., of the Adrenal Bodies

There is nothing very special or characteristic in the *proteins* which can be extracted from the adrenal bodies. They consist of the albumins, globulins, and nucleo-proteins which are found in animal tissues generally.

The *extractives* and salts, moreover, do not call for any special mention.

The subject of the occurrence of *choline* in animal tissues has already been sufficiently dealt with (p. 25 *et seq.*). It is probable that we are justified in considering that whatever

[1] It has been stated that in cases of sudden death the adrenals contain more adrenin than in cases of gradual death. This observation, if it can be confirmed, may be of considerable medico-legal importance.

choline may be present in the adrenal bodies is of no special functional significance.

The *lipoid substances* contained in the cortex of the adrenal body are possibly of considerable importance, and their chemical nature may yet reveal the secretory function of the cells of this part of the adrenal gland. Their presence in the cells has been known to histologists and morphologists for a long time, but attempts to deal systematically with their chemistry are of recent date. So far as they are involved in a treatment of the microscopic structure of the adrenal cortex, they will be discussed in a later section of this work (p. 239). At this stage it will be desirable to state what is known of these substances from a more purely chemical standpoint.

According to Fränkel, the different organs of the body contain different lipoids, which are characteristic for each particular organ. The difference between the lipoids of various organs on the one hand and the lipoids of the same organ in different groups of animals vary both qualitatively and quantitatively.

Biedl has devoted special attention to the lipoids of the adrenal bodies of the pig. He finds that the glands contain 74·61 per cent. water and 25·39 per cent. of dry substance. Of this dry substance, 61·12 per cent. consists of protein, and 38·88 per cent. lipoids and extractives. It is pointed out that since the extracts were made from the whole gland, the cortex must contain a much greater proportion of lipoids. In order to prove this point definitely it is proposed to investigate the inter-renal body (which consists of cortex only) in the Elasmobranch fishes.

Thus we see that the adrenals must be placed among the organs richest in lipoids, since a third of the total dry substance is made up of these materials. Among the definite chemical compounds recognized by Biedl in the adrenal extracts are cholesterinpalmitate [$C_{27}H_{45}O$ $(C_{16}H_{31}O)$], the cholesterin ester of carnaubic acid [$C_{27}H_{45}O$ $(C_{24}H_{47}O)$], and kephalin.

According to Biedl, it appears probable that the cholesterin esters are specific for each particular organ and perhaps for each particular species, but not that they are to be regarded as a definite secretory product of the gland.

Q. The Medical and Surgical Employment of Adrenal Preparations

After the observation of Oliver, that an artery in the frog's mesentery is contracted by adrenal extract to such an extent that blood ceases to be driven through it, he began to use the extract as a styptic in his experimental operations; its application for this and similar purposes is now general.

Surgical Employment of Adrenin alone or combined with other Drugs.—A subcutaneous injection of adrenalin solution (1 in 10,000) produces a bloodless condition of the tissues quite as readily as the method of bandaging or freezing. If adrenalin is combined with cocaine for subcutaneous injection, it is found that the effect of the cocaine is increased and lasts for a longer time. A combination of adrenalin with eucaine is also found to be very beneficial. It is stated that the toxic effects of cocaine are to a certain extent neutralized by the simultaneous employment of adrenalin.[1]

Braun has made extensive use of this method, employing the following solution: 100 c.c. of a 0·05 per cent. solution of cocaine hydrochloride, using 6 per cent. sodium chloride solution as a solvent, to which 3 to 5 drops of adrenalin hydrochloride (1 in 1,000) are added; the dose is 50 c.c. to 100 c.c. The operation may be performed ten minutes after the injection. The lower part of the rectum may thus be rendered insensitive, and operations for fistulæ or hæmorrhoids, or dilatation of the sphincter, may be performed in a painless manner. The method may also be used for excision of a piece of rib, for operations on the scalp, for removal of sebaceous cysts, for amputation of a finger, etc.

Major operations under spinal anæsthesia produced by 1 in 2,000 adrenalin solution in conjunction with 0·0075 to 0·015 gramme cocaine, have also been performed without ill effects.

Honigmann uses β-eucaine instead of cocaine for local anæsthesia. The use of cocaine and adrenalin combined is also recommended by several other authors.

[1] Novocaine is now frequently employed.

Barker recommends the following formula :

Distilled water	100 c.c.
β-eucaine	0·2 gramme.
Sodium chloride	0·8 gramme.
1 pro mille adrenalin chloride solution	♏x.

The actual strength of adrenalin in this solution is one in two hundred thousand (1 : 200,000). On production of local and regional anæsthesia by means of this fluid, Barker has performed the following operations with the most satisfactory results : (1) Amputation through the knee-joint for gangrene of the foot due to diseased arteries and diabetes ; (2) abdominal section and opening of the stomach and jejunum in search of a source of severe bleeding (not found) ; (3) removal of a cyst of the thyroid ; (4) Bassini's radical cure of inguinal hernia ; (5) removal of a silver wire from round the patella.

Equally favourable results are recorded by other surgeons. Local anæsthesia produced by the combined use of adrenalin and cocaine, or β-eucaine, has also been employed in gynæcological operations besides those involving abdominal section. The method has been found useful in operations for prolapsus uteri and plastic operations on the vagina ; owing to the anæmia produced by these solutions, they were serviceable also in amputation of the cervix.

Application of Adrenal Preparations to the Conjunctiva and other Mucous Surfaces.—Oliver found that a congested and inflamed conjunctiva is at once rendered pallid under the influence of adrenal extract. The use of adrenal derivatives in ophthalmological operations and examinations has been attended with great advances in this department. In various operations on the eye the field of operation may be kept free from blood by the use of adrenalin solution, 1 to 50 drops of a solution of the strength of 1 in 5,000, or 1 in 10,000. Darier recommends the following solution for the purposes of removal of a foreign body from the eye, cauterization, etc. : 10 drops of a solution of adrenalin hydrochloride (1 in 1,000) ; cocaine hydrochloride, 0·1 gramme ; distilled sterilized water, 10 grammes. Adrenal extracts whiten the conjunctiva in trachoma, conjunctivitis, keratitis, iritis, and other conditions. An eye with a foreign body on the cornea is whitened. During operations on the ocular muscles, tenotomy, and advancement, the extract whitens the eyeball ; the astringent effect is

temporary, and there is no subsequent congestion. The local action of adrenin is very evanescent, and the application has to be repeated every four or five minutes.

In diseases of the nose and throat adrenal preparations have found a useful application.

Adrenal preparations are also employed for rhinological purposes. The marked ischæmia produced is most useful in revealing causes of obstruction. It has been used as a hæmostatic with good results, also in hay fever, epistaxis, and, paroxysmal sneezing and rhinorrhœa.

A solution of cocaine and adrenalin is very generally employed for the painless extraction of teeth.

In bronchial asthma adrenalin applied to the nasal membrane has been used for some years. Kaplan has more recently employed subcutaneous or intravenous injection (5 to 15 minims of the 1 in 1,000 solution). Miller reports favourably on the drug administered in one of these ways for bronchial asthma; the relief was considerable, but in no cases could he observe any curative effect. On the other hand, there were no untoward results. It is not known how the beneficial effect is produced in these cases—perhaps it is due to inhibition of the bronchial musculature. But Miller is inclined to think that the results point to the pathology of bronchial asthma being due to a hyperæmia of the bronchial membrane.

Use of Adrenal Preparations in Diseases of the Bladder.—Braun recommends a mixture of adrenalin and cocaine for injection into the bladder preparatory to a cystoscopic examination. Adrenalin has been found useful in catheterization for urethral stricture. Adrenin has also been successfully employed to relieve bleeding in the urinary tract and in atony of the bladder.

The Use of Adrenal Preparations and of Adrenin in Hæmorrhages.—Clinical experience has shown that when hæmorrhage occurs from a surface to which adrenin may be applied, relief is prompt, and in the large majority of cases, lasting. The drug then finds ready application in epistaxis, bleeding from granulating wounds, and in cases of tears of the cervix uteri, and in many other similar cases.

Schäfer believes that when adrenin is given by the mouth there is "very distinct evidence of vascular constriction, for bleeding from internal parts, such as the stomach, intestine,

bladder, and uterus, and even the bleeding of post-partum hæmorrhages, may thereby be effectually controlled." The explanation offered is that injured vessels are more susceptible to the extract and react to a slight excess of it in the blood more readily than do normal vessels. But Miller considers that as regards vessels not accessible to local applications the constrictor action of adrenin is more than counterbalanced by the sudden increase of general blood-pressure. He states that in rabbits he has observed that in a wound the vessels that have stopped oozing often start bleeding after an intravenous injection of adrenalin. In pulmonary hæmorrhage, he thinks, there is the additional danger of possible absence of vasoconstriction, and therefore the bleeding might increase by having a condition of dilated vessels with increased pressure. Schäfer replies to this that administration by the mouth does not perceptibly raise the systemic blood-pressure, and that, nevertheless, there is considerable clinical evidence that internal hæmorrhages, when not too profuse nor coming from large vessels, may be brought under control by oral administration, especially if, as he suggests, the extract has a greater effect upon injured vessels.

The question just discussed, naturally, is of great import in relation to the treatment of hæmoptysis. Batty Shaw inclines to the view that hypodermic or oral administration of adrenin can have little effect upon bleeding occurring from destructive tuberculous disease of the lungs, and he attaches comparatively little importance to the clinical reports which so far have been published, and in which it is impossible to say that the good results were not due to other factors.

Quite recently Wiggers has investigated the value of adrenalin in inaccessible internal hæmorrhages. He concludes that large doses of the drug (0·05 to 0·1 milligramme) cause a short preliminary increase of hæmorrhage followed quickly by a decrease or cessation of bleeding. On account of the great preliminary loss of blood, they are always contra-indicated. Small doses (0·01 to 0·025 milligramme) cause little or no preliminary increase, but shorten the course of hæmorrhage. As they save the red blood cells in every way, they are therapeutically desirable. Continuous intravenous injection of weak solutions maintains a slight elevation of pressure, and hæmorrhage is simultaneously checked. This can also be

accomplished by intramuscular injections. Adrenalin is not indicated in all intestinal hæmorrhages. The condition of the blood-pressure is the criterion for its use. In hæmorrhages of short duration, when the pressure has not fallen to any extent, a judicious dose of nitrites proves of more benefit than adrenalin. When the bleeding has been profuse, however, and a low pressure already exists, it becomes vital that hæmorrhage should be checked without further reduction of pressure. Adrenalin finds its use in this field. The use of adrenalin should always be closely followed by blood-pressure observation. A dose sure to be below the safety limit should first be tried and the pressure carefully estimated. If no rise occurs, gradually increasing doses may be injected until a slight elevation of pressure is present, in which case we may be certain that enough has been introduced to affect hæmorrhage, and at least no significant preliminary increase has resulted.

Adrenin in Cardio-Vascular Conditions.—In cardio-vascular conditions adrenin is most distinctly indicated when there is marked vasodilation and the heart muscle is in good condition. These indications are present in chloral-poisoning, shock, and asphyxia. Gottlieb pointed out that when a rabbit has received increasing doses of chloral until the heart comes to a standstill, adrenal extract will start the heart beating and maintain it for from twenty to thirty minutes. He considers that adrenalin is superior to digitalis for this purpose. Crile strongly advocates the use of adrenalin in "surgical shock," and although good results have been stated to accrue from its employment in ether-poisoning, yet, according to Schäfer and Scharlieb, it is of little avail to restore a heart paralyzed by chloroform.

In the cardiac insufficiency of diphtheria—in which disease, as Elliott and Tuckett have shown, there is a deficiency of chromogen in the adrenal medulla—Gottlieb has reported that adrenin administered intravenously is of temporary benefit. The same applies to phosphorus-poisoning. Schäfer suggests that administration by the mouth or subcutaneously, having a slower effect, might be beneficial in such cases. Rolleston has recently discussed the value of adrenalin in such cases as the cardiac failure of diphtheria, and lays stress, as others have done, upon the possibility that the increase of the peripheral resistance may give the failing ventricle more work to do.

He states, however, that he has for some time been in the habit of giving adrenalin by the mouth in cases of pneumonia in adults, and in broncho-pneumonia in children. In these cases it appears to prevent cardiac failure, and has not given rise to any bad symptoms such as œdema of the lungs. He mentions, however, the possibility that such administration of adrenalin may give rise to arterial degeneration.

Adrenal extract is stated to be useful in functional disorders of the heart associated with lowered arterial tension. In certain cases, therefore, it may be indicated in migraine and neurasthenia, where these disorders are associated with a low blood-pressure.

Kauert has quite recently recommended the use of synthetic suprarenin in medicine. He reports that it is useful in cases of vasomotor paralysis, and may be used both therapeutically and prophylactically. The dose is from 1 to 6 milligrammes subcutaneously, $\frac{1}{4}$ to 1 milligramme intravenously. The drug is contra-indicated in organic heart disease, nephritis, and arterio-sclerosis with high blood-pressure.

Adrenal Preparations in Addison's Disease.—The clinical evidence as to the value of adrenal extracts and preparations in the treatment of Addison's disease is very conflicting. A cure can, indeed, scarcely be expected by treatment directed towards remedying adrenal inadequacy, for the reason that this inadequacy is only one result of a tubercular or malignant disease, or a definite atrophy of the gland. Shaw points out that there are several other reasons why such treatment should fail. Among these he mentions our ignorance of the functions of the cortex of the gland and the difficulty of securing the absorption of an adequate amount of adrenin.

The beneficial results which have been alleged are to be found chiefly in diminishing the weakness and sense of lassitude. Numerous cases have been treated with varying degrees of success.

Rolleston refers to cases of chronic adrenal inadequacy, or "Addisonism." Boinet recommends adrenalin in these cases. Various diseased conditions, such as cyclical albuminuria, neurasthenia, with low blood-pressure, purpura, status lymphaticus, and hæmophilia, have been attributed to adrenal inadequacy, and hence adrenalin has been recommended. But in these cases, as in those of Addison's disease, it seems

very unwise to administer simply the pressor substance extracted from the medulla. In the present state of our knowledge it would be far more desirable to give either the fresh whole gland or extracts prepared from the whole gland, both cortex and medulla. The pigmentation in Addison's disease has probably never been experimentally induced, and certainly has never been satisfactorily explained, and we are in the dark as to whether this, one of the most striking symptoms of the disease, is due to a lesion of cortex or of medulla, or is due to damage to both.

We have seen that the results of treatment of Addison's disease by means of adrenal gland substance are—as compared with the effects of thyroid treatment in myxœdema—distinctly disappointing, though it may be that in some instances good results have been obtained. Dr. Byrom Bramwell, who regards the symptoms of Addison's disease as partly due to glandular inadequacy, and partly the result of irritation of the sympathetic in the neighbourhood of the adrenal bodies, explains the failure of the extract in some cases by supposing that in these instances there are adhesions to the sympathetic plexus and irritation of it; while the cases which react satisfactorily to the extract are those in which there is only glandular inactivity or inadequacy.

Rolleston says: "It should be remembered that the medulla alone contains the active physiological principle, the cortex appearing to be inert, and that the extract is at present largely made from the whole gland, and not, as would be physiologically more correct, from the medulla alone. This must lead to a certain amount of uncertainty as to the amount of active principle contained in any pill or tabloid." It will be gathered from what has been said above (p. 152) that it appears to the present writer that it is far from certain that it would be "physiologically more correct" to give extracts made from medulla only, or to give, as would probably be suggested at the present time, pure adrenin. It seems safer, in view of our ignorance of the precise pathology of the disease, to give an extract made from the whole gland, or, better still, if administration by the mouth be considered advisable, the fresh minced gland. Because the medulla is the only part which yields a powerful active substance to extracts, we must not assume that it is the only part concerned in Addison's disease,

Various Applications of Adrenal Preparations and of Adrenin.—Barr found that after withdrawal of fluid from the pleural cavity of a patient suffering from carcinoma of the lung, the fluid did not accumulate again after the introduction of adrenalin. The same applies to tuberculous pleurisy, tuberculous and malignant peritonitis, and to ascites due to cirrhosis. The method was, after removal of the fluid, to inject 40 to 60 minims of adrenalin chloride, 1 in 1,000. In ascites the success was not so great as in the other cases.

Plant and Steele report good results in cirrhosis of the liver and pleural effusion, and state their belief that the injection of adrenalin chloride is strongly indicated in all cases of serous effusion when simple tapping does not effect a cure. The empirical results obtained by Barr and others are explained by the experiments of Exner and Meltzer and Auer. Exner found after experimental injection of adrenalin that absorption of strychnine and physostigmine is delayed, and so the life of the animal may be saved. This was confirmed by Meltzer and Auer, who also showed that fluorescin transfused from the blood into the peritoneum much more slowly in animals that had previously received adrenalin intravenously. It has also been demonstrated that intraperitoneal injection of adrenalin will lessen the tendency of transudation into the peritoneal cavity, after excessive transfusion of normal salt solution.

Milian states that certain symptoms due to salvarsan can be prevented by previous intramuscular injection of adrenin.

Jona recommends adrenin in the emergency treatment of non-corrosive poisoning by the mouth (cyanide, strychnine, aconite), on the ground that it diminishes the rate of absorption.

Mode of Administration of Adrenal Preparations.—It is well to recall that adrenal extracts were first administered by subcutaneous injection. But since Oliver and Schäfer reported that the activity of the gland is not impaired *in vitro* by pepsin and hydrochloric acid, it has become customary to give it by the mouth. Raw sheep's adrenal bodies have been given, and a tincture has also been employed, but most usually a dried extract is employed in the form of a pill. In addition to these modes of exhibition all the various forms of the active substance adrenin have been used from time to time.

Some years ago the present writer failed to observe any

physiological effects upon dogs, cats, and rabbits of feeding with the adrenal bodies of the sheep, and the administration of large doses of extracts (in some cases made from medulla only) failed to produce any noticeable rise of blood-pressure in the human subject. But Leyton states that adrenal extract, although when administered by the mouth it ordinarily fails to produce elevation of blood-pressure, will bring about this effect in cases of Addison's disease. However this may be, the most certain method by which to obtain any definite pharmacodynamical effects is that of subcutaneous, intramuscular, or intravenous injection. The intravenous method should be employed in all cases of extreme emergency, such as ether-poisoning and heart failure in diphtheria.

Miller urges that adrenin ought to be employed with great care in all patients with suspected arterial degeneration, and in elderly people. The danger of causing glycosuria in the human subject does not appear to be great.

R. Theories as to the Function or Functions of the Adrenal Bodies

Our scientific knowledge of the adrenal bodies may be said to date from the year 1855, when Addison published his famous work. The known facts about the organs in question are, very briefly stated, as follows : Disease of the glands gives rise to a characteristic train of symptoms, among which are pigmentation of the skin and extreme muscular weakness. Extirpation of both adrenal bodies is a very dangerous operation, and, according to the majority of investigators, invariably leads to death. It is the cortex and not the medulla which is essential to life. Extracts of the medullary portion of the body are toxic when administered to an animal subcutaneously, intramuscularly, or intravenously, among the symptoms being glycosuria and degeneration of the arteries. Intravenous injection produces a powerful effect upon the heart and blood-vessels, and is chiefly manifested by a very marked rise of the arterial blood-pressure. The general pharmacodynamical effects are strikingly similar to those brought about by a stimulation of the sympathetic nervous system ; these physiological or pharmacological effects are obtained only by administering extracts of the medulla, the cortex being inactive.

Comparative anatomy and comparative physiology reveal

the fact that the medulla of the adrenal body is not the only representative of the tissue which forms it (chromaphil tissue); there are numerous scattered bodies of the same nature in close relation to the sympathetic ganglia and nerves in different regions of the body. In lower vertebrate animals the medulla (chromaphil bodies) and cortex (inter-renal bodies) form two separate and independent systems, having no anatomical (and, so far as we know, no physiological) relationship to each other. Indeed, strictly speaking, the medullary substance is not part of the adrenal body at all, but simply an accumulation of the chromaphil tissue which has arisen from the sympathetic in a certain region of the body, and has insinuated itself into the adrenal proper, or what we call the "cortex."

In discussing the function or functions of the adrenal bodies these facts of comparative anatomy must not for a moment be lost sight of. The ultimate question which we have to solve is, from the standpoint of comparative physiology, not so much what is the function of the adrenal body or of its two constituent portions, but what are the functions respectively of the inter-renal system (cortical system) and the chromaphil system (medullary system), which are, as we have seen, separate and distinct in Elasmobranch fishes (Figs. 44, 45)? It is difficult to say whether we ought to expect that these functions should be of a kindred nature, or in any way related to each other, in the case of the mammals. There certainly would be no *a priori* reason for suspecting the existence of any such relationship in the Elasmobranch fishes, but we cannot overlook the fact that phylogenetically and ontogenetically portions of the two systems become attracted, so to speak, to each other, and finally in the adult mammal form a single compound organ. One cannot escape from the suspicion that the coming together may have some significance affecting the functions of the gland as a whole. We are, however, at present completely in the dark as to any functional correlation between the two constituents. It is possible, moreover, that cortex and medulla have separate and distinct functions; at any rate, most of the accurate knowledge which we possess and nearly all our most plausible hypotheses have reference to the medulla of the organ, and this notwithstanding the fact that the cortex is larger than the medulla, and more distinctly glandular in type and appearance.

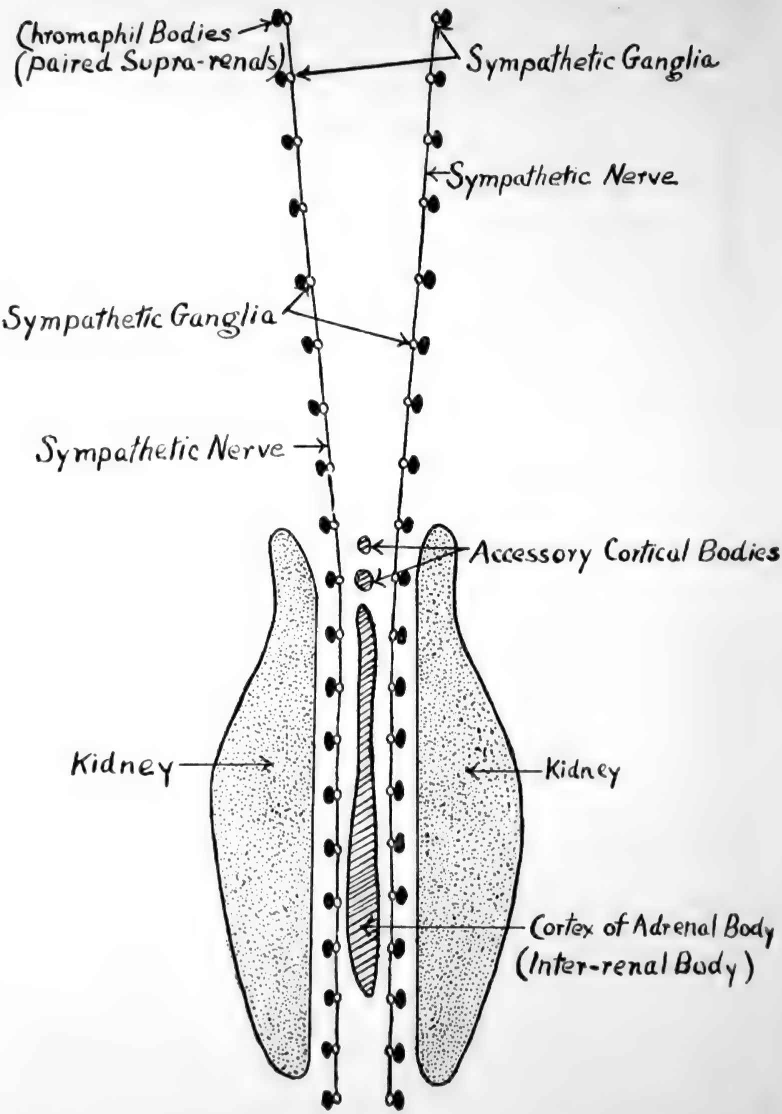


FIG. 44.—Diagram of the adrenal representatives in Elasmobranch fishes showing the cortical gland (inter-renal body) and the medullary glands (chromaphil bodies, "paired suprarenals") in relation to the sympathetic and the kidneys.

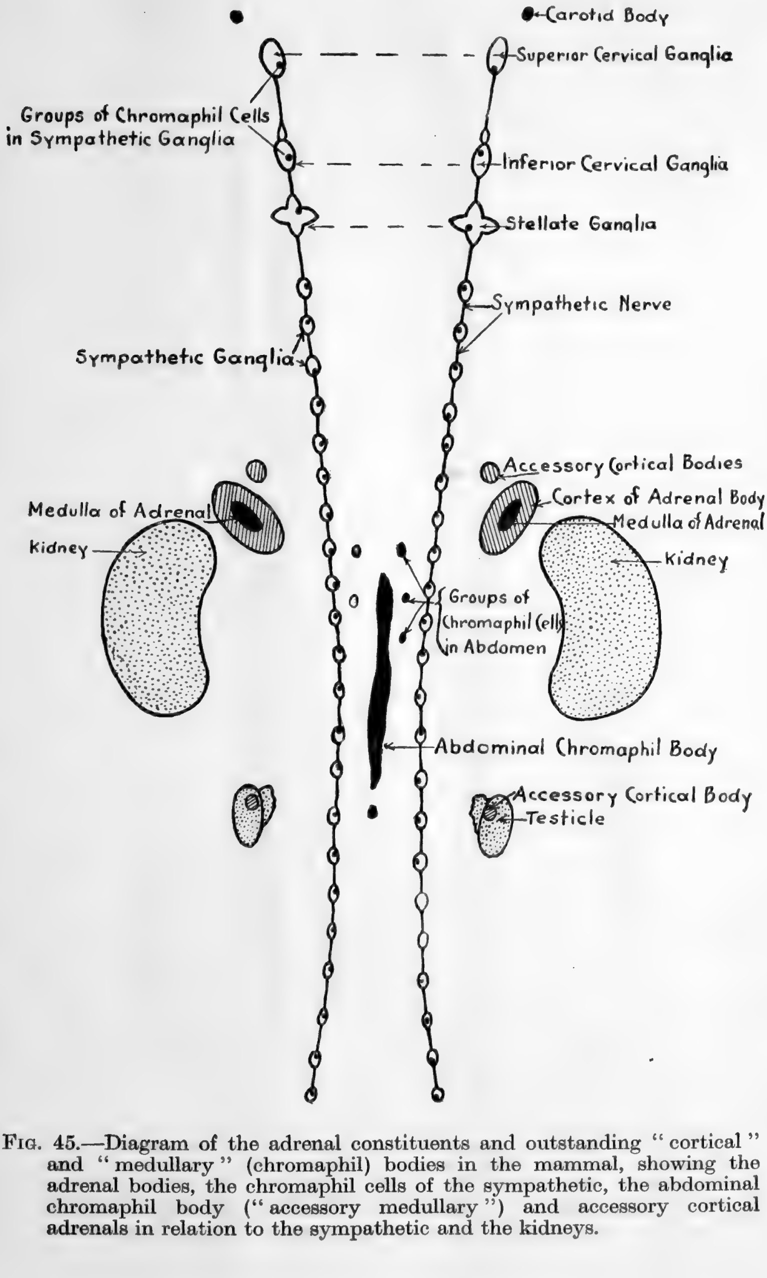


FIG. 45.—Diagram of the adrenal constituents and outstanding "cortical" and "medullary" (chromaphil) bodies in the mammal, showing the adrenal bodies, the chromaphil cells of the sympathetic, the abdominal chromaphil body ("accessory medullary") and accessory cortical adrenals in relation to the sympathetic and the kidneys.

1. *Theories as to the Function of the Medulla*

Prior to the discovery of the active principle of the medulla of the adrenal body, some authors considered that the gland had an excretory function. Thus, MacMunn found hæmochromogen in the gland, and especially in the medulla, and drew the conclusion that in the adrenals a downward metamorphosis of worn-out pigments—hæmoglobins and histohæmatins—is taking place, and that the function of these organs is to pick out of the circulation these worn-out or effete colouring matters with their accompanying proteins. Others considered that the waste products of muscular metabolism are eliminated by the glands. Still others attributed a blood-destroying function to the gland. But since the discovery of the pressor principle the excretory theory has almost entirely been replaced by that of secretion—internal secretion.

It is now generally admitted that most, if not all, of the recognized effects produced by the administration of adrenal extracts are to be ascribed to the adrenin which is contained in them. Three questions immediately arise : Is adrenin to be looked upon as the product of the secretory activity of the medulla of the glands ? Is it actually poured out into the blood-stream ? Supposing these questions to be answered in the affirmative, then what is the use of this internal secretion —this hormone—in the animal economy ?

Kohn, from morphological considerations, is opposed to the view that the chromaphil tissues have an internal secretion. He is certainly justified in insisting that we have no right, simply because adrenin has certain pharmacodynamical effects, therefore to assume, without further definite evidence, that it is one of the functions of chromaphil tissues to pour out this substance into the blood-stream in order that it may produce such effects upon certain tissues of the body. He considers that the cells forming the medulla of the adrenal body and the chromaphil tissues elsewhere are not "epithelial," and therefore cannot secrete.

But the active substance of the adrenal medulla is of a very exceptional and extraordinary character, and is not to be classed with the less active bodies found in extracts of organs and tissues generally, and the medulla of the adrenal body is not a mass of chromaphil cells of irregular shape and indefinite

arrangement, but an organ arranged in the form of definite columns of cells, with intervening blood-spaces—in fact, a "gland." It is therefore *a priori* probable that the adrenal medulla may secrete into the blood-stream an active material which is of benefit to the economy. Again, a careful comparative study of the chromaphil tissues in general, and the adrenal medulla in particular, has led to the conclusion that the latter is probably to be regarded as a specialized development of the former (see p. 116).

Considerable evidence has, however, been accumulated that adrenin under certain conditions is secreted through the adrenal veins into the general blood-stream. It has been stated by several authors that the blood of the adrenal vein contains a sufficient amount of the active principle of adrenal extract to produce marked rise of blood-pressure when intravenously injected. This, however, has not been confirmed.

Ehrmann, basing his investigations upon the discovery of Lewandowsky, and relying upon the observations of Meltzer and Auer that frogs, after adrenin injection, show a maximum dilatation of the pupil, worked out a method for the estimation of adrenin. He used the enucleated frog's eye, as recommended by Meltzer and Auer, and measured the amount and rapidity of widening of the pupil on placing the eye in adrenin solution. By this method it could be shown that the blood coming from the adrenal bodies contains the active substance, adrenin, and Ehrmann concludes that it passes into the blood as a physiological secretion. Pilocarpine and atropine lead to no marked increase or diminution. In diphtheria intoxication it is somewhat increased. Raising or lowering the blood-pressure has no effect on its amount, which varies considerably in different animals. According to Ehrmann, the rabbit pours into its adrenal veins adrenin in a concentration of between 1 : 1,000,000 and 1 : 10,000,000. There is a parallelism between the amount secreted and the sensibility of the animal to the action of the substance.

Waterman and Boddaert, however, have shown that the mydriatic action on the enucleated frog's eye is not absolutely specific for adrenin. Gautier says that the solutions employed must be faintly acid, since dilute alkali in sodium chloride solution gives by itself a positive result. Schultz says that the time taken for a certain degree of widening is of more value than the extent

of total dilation. The method is now considered by Meltzer to be untrustworthy, as the amount of adrenin necessary to produce an action upon the frog's eye varies not only in different frogs, but even in the two eyes of the same frog. Trendelenberg now uses the method of perfusion through the vessels of the hind-limb of the frog. Ritchie and Bruce, using the bichromate coloration and the blood-pressure testing, have recently reported (contrarily to Ehrmann) that in diphtheritic toxæmia in guinea-pigs there is complete exhaustion of all adrenin from the medulla of the adrenal bodies.

Another test for adrenin in the blood consists in injecting hypertonic solutions into the auricular vein, and noting the occurrence of glycosuria. It was found that this, like the diabetic puncture, also renders the serum mydriatic. It is considered that these experiments show that adrenin stimulates the sympathetic. It is believed also the sympathetic may be stimulated by means of thyroid material, and, on the other hand, stimulation of the sympathetic leads to increased secretion of the thyroid.

An elaborate series of metabolism experiments by Eppinger, Falta, and Rudinger have been regarded as pointing to a definite internal secretion on the part of the adrenal medulla, or rather of the whole chromaphil system, and a functional relationship between adrenal body, thyroid, and pancreas through the medium of the sympathetic nervous system. A relationship between pancreas and adrenal body in regard to hyperglycæmia is indicated by the experiments of Zuelzer and others. Ritzmann claims that the degree of glycosuria depends on the quantity of adrenin present in the blood at any given moment. But the quantitative result of this observer cannot be regarded as correct, since it has been proved by Underhill that the glycosuria obtained by Ritzmann with small doses of adrenin, intravenously administered, was dependent on the use of urethane as the anæsthetic. Adrenin introduced in very dilute solutions (1 : 500,000 to 1 : 125,000) fails to induce glycosuria in the normal rabbit. On the other hand, when the animal is under the influence of urethane narcosis, these dilute adrenin solutions are a sufficient stimulus for the production of glycosuria. It seems, then, that urethane renders a rabbit unusually sensitive to the glycosuria-inducing action of adrenin. The subcutaneous administration of adrenin in a

dilution of 1 : 1,000 to normal rabbits is far more efficacious in causing glycosuria than the same quantity of adrenin introduced intravenously in much greater dilution. The same quantity of adrenin injected subcutaneously at different periods into the same animal under constant conditions causes the appearance in the urine of variable quantities of sugar.

Underhill and Fine have discovered that subcutaneous administration of hydrazine is capable of preventing the appearance of sugar in the urine of dogs from which the pancreas has been removed. They suggest that hydrazine has an action upon sugar metabolism entirely similar to that exerted by the internal secretion of the pancreas. According to this idea, injections of hydrazine cause hypoglycæmia by increasing the efficiency of the pancreatic secretion or by augmenting its output. They find definitely that the secretion of adrenin is not notably inhibited by hydrazine.

As a working hypothesis, the authors make use of the scheme of interaction between the pancreas and the adrenal bodies given on page 220.

Ringer has brought forward some results which indicate that adrenalin, by its constricting effect on the bloodvessels, produces anæmia of the tissues, resulting in imperfect oxidation, and this anæmia is followed by the conversion of glycogen into dextrose, by hyperglycæmia, and consequently by glycosuria.

In 1891 Jacobi described nerves branching from the splanchnics, and supplying the adrenal bodies. The same observer, in his experiments on the nervous functions of the adrenals, without, of course, having any knowledge of the pressor effects of extracts, reports that in two experiments stimulation of the gland itself produced a rise of blood-pressure. But Apolant, in a series of more than thirty experiments upon rabbits, could obtain no such result. Biedl found that stimulation of the splanchnics or the ramus suprarenalis gives rise to vasodilation, and suggested that this is accompanied by increased secretion from the gland. We must consider, however, the result open to question, as no test of the active principle was made, but only a study of changes in certain granules in the blood of the adrenal vein (*vide infra*).

More definite results were obtained by Dreyer, who records that the physiological action of the blood from the adrenal vein

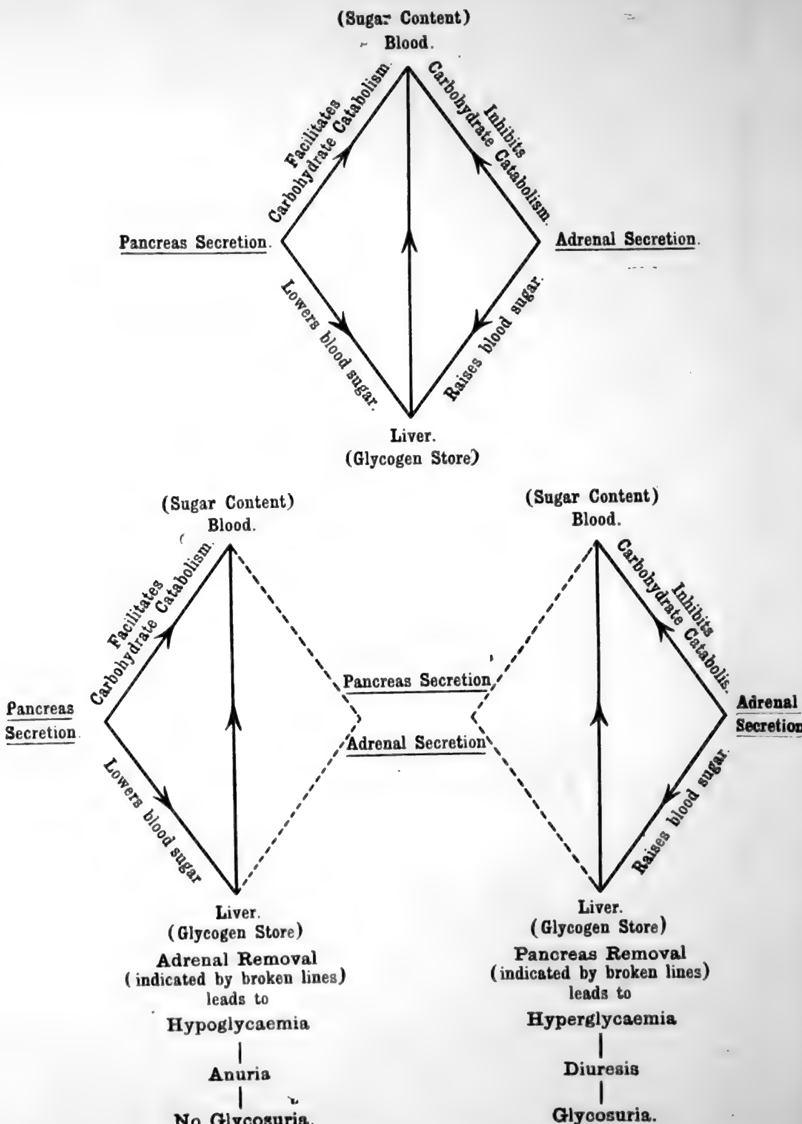


Diagram indicating influence of the organs on the metabolism of carbohydrate (Underhill and Fine).

during splanchnic stimulation is greater than that of the same blood under normal conditions. He looks upon the splanchnic as a true secretory nerve for the adrenal body.

After the very important discovery that adrenal extracts raise the blood-pressure, there was a growing tendency to assume that the function of the adrenal (or, at least, of its medullary portion) is to help to maintain the normal blood-pressure and to keep up the tone of sympathetically innervated structures in general. The present writer was one of the first to grow suspicious on this point. If the constant secretion of adrenin into the blood-stream and its action upon the sympathetically innervated vascular muscle is an important factor in the maintenance of the normal blood-pressure, then it ought to be possible by tying or clamping the veins issuing from the glands, to keep down the blood-pressure at a low level during the period of clamping or tying, and to allow it to reach its normal level on releasing the clamp or the ligature. Some writers have claimed that they have obtained this result. Such has been definitely recorded by Strehl and Weiss, who extirpated the adrenal body on one side, and found that when a clamp was put upon the adrenal vein of the other side the blood-pressure immediately fell, and rose again when the clamp was released. Their experiments were performed upon rabbits. They gave a tracing which shows a very marked depression during the period of the clamping of the vein.

Kretschmer finds that if adrenalin solution is injected intravenously into rabbits each new dose produces a rise of pressure, and between the doses the pressure falls to normal owing to the rapid destruction of adrenalin in the body. For this reason repeated injections cannot keep up the blood-pressure, but *continuous* injection *can* do so. The action on the blood-pressure lasts just so long as there is any adrenalin in the blood. According to Kretschmer, the continuous internal secretion of adrenalin from the adrenal bodies is probably of significance for the maintenance of the normal vascular tone. If, as *in vitro*, the destruction of adrenalin in the body is dependent on the amount of alkali present, then should intravenous injection of alkali cause a lowering of blood-pressure due to a breaking down of the continuous supply of adrenalin. A lengthening of the action of adrenalin is in fact produced experimentally by a simultaneous injection of nitric acid.

At the suggestion of the present writer, the experiment of Strehl and Weiss has been repeated by Young and Lehmann. In their experiments an attempt was made upon dogs to dam back any secretion which the glands may pour into the blood-stream, and after an interval to remove the obstruction and allow the accumulated adrenin to flow into the general circulation. A cannula was inserted into the carotid artery, the adrenal glands were exposed through an abdominal incision, and a double ligature passed beneath the organ on each side; the ligatures were tied on each side of the gland above the vein, so as to form two pedicles. The ligatures were left in place for from ten to thirty minutes, and then released, and the tracing continued. Out of eight experiments, there was no effect on the blood-pressure in three; in two there was a slight rise after releasing the ligatures; in the remaining three there was a decided rise of pressure (similar to that which follows the injection of the extract), lasting about three minutes. In one case the effect was repeated by tightening the ligatures a second time, and again releasing them.

It is important to note that in these experiments after tightening the ligature there was very little, if any, fall of blood-pressure. In fact the experiments merely show that adrenin is poured out into the adrenal veins.

Dr. Young repeated these experiments and found that even after the lapse of several hours with the blood from the adrenal bodies absolutely excluded from the circulation, there was no appreciable fall of blood-pressure. Austmann and Halliday have also at my suggestion performed a series of experiments in which the adrenals were removed or whose vessels were tied off while the blood-pressure was continuously recorded for many hours. It was found that when the experiment was continued until the animal died the blood-pressure curve was not appreciably different from that obtained from an animal simply kept under ether as long as possible. These experiments appear to show conclusively that the secretion of adrenin into the circulation is not to be regarded as a factor in the maintenance of the normal blood-pressure.

But there is another argument which militates powerfully against the theory just mentioned. It was shown by Moore and Purinton that very small doses of adrenin will *lower* the blood-pressure, not raise it, so that the amount of adrenin

which is normally poured out by the adrenal veins would tend to keep the blood-pressure down rather than up.

Stewart and Rogoff have given another proof that the discharge of adrenin from the adrenal bodies is not indispensable for life and health. When one gland is removed from a cat and the secretory nerves to the other are cut the animal appears to suffer no ill-effects. Now in this case adrenin could scarcely have been present in the blood in a concentration of more than one part in four millions, which, as Stewart observes, "the most enthusiastic upholder of the physiological importance of adrenin will probably consider below the threshold of any definite physiological reaction. Yet the animal was in good health."

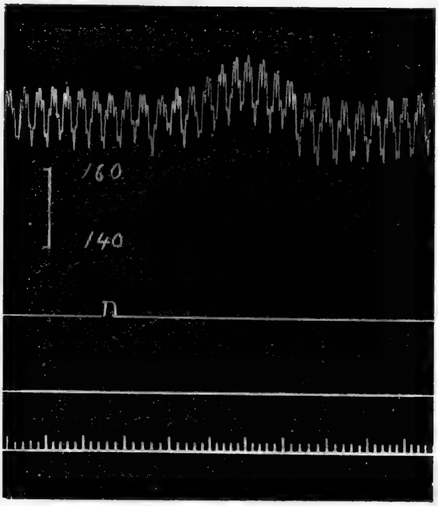


Fig. 46.—This tracing shows the rise of blood-pressure due to release of pressure on adrenal vein. The vein has been compressed for some time, and was released at the point signalled (Gardner and Gunn).

Hoskins is of the opinion that there is no reliable evidence that under normal conditions circulating blood contains any adrenin at all. He points out that as the technique of investigation has improved the reported dilution of the adrenin in arterial blood has constantly approached infinity.

The subject of adrenal secretion has been investigated by Asher and Tscheboksaroff. Asher performed his experiments upon rabbits. All the arteries coming off from the abdominal aorta and supplying the viscera, with the exception of those running to the adrenal bodies, were ligatured, and then all the abdominal organs, excepting the liver and the adrenal bodies, were extirpated. The blood was squeezed out of the veins, and the portal vein tied off. Electrodes were then placed under the two splanchnic nerves, the spinal cord was

cut across high up, and artificial respiration carried out. The blood-pressure was recorded from the carotid or the femoral artery. Stimulation of the splanchnic nerves gave rise to a marked rise of blood-pressure, and continuous stimulation produced a long-continued elevation of pressure. The rise did not occur if the adrenal veins were tied.

Tscheboksaroff has reached the same conclusions as Dreyer did—viz., that the great splanchnic nerve in dogs is the true secretory nerve of the adrenal body, and that its stimulation leads to an increase of the adrenin which is found in the venous blood. Section or ligature of this nerve diminishes the amount of adrenin in the blood.

The theory that the chromaphil tissues (and especially the medulla of the adrenal bodies) maintain, or help to maintain, the normal tone of the bloodvessels and other sympathetically innervated structures, has been already discussed. Evidence has also been given that the medulla of the adrenal body is not essential to life, and that the reduction of the adrenin content of the blood to a minute fraction of the normal amount does not affect the health of an animal.

These statements, however, do not exclude the possibility that the chromaphil tissues play a part in certain reactions which are initiated elsewhere, as, for example, in those which result from stimulations of nerves in laboratory experiments.

We have referred above to certain experiments involving stimulation of the splanchnic nerve, and its effect on the blood-pressure. This question must now be treated in greater detail.

It has been known for a long time that the rise of blood-pressure brought about by stimulation of the peripheral end of the splanchnic nerve is not simple. The curve obtained suggests at once that there is more than one factor concerned in its production.

Johansson found that in the dog the curve presents two summits, and it has since been found that the same is generally true in other animals also.

Lehndorff also worked with dogs and came to the conclusion that the first rise is due to vasoconstriction in the splanchnic area, the " step " to a temporary dilation of the heart, and the second rise to increased force and frequency of the heart-beat accompanied by vasoconstriction in the somatic area.

Elliott, who investigated the subject in cats, stated that in

animals recently admitted and still in a frightened condition, the typical splanchnic curve cannot be obtained. But he regarded the typical curve as something different from that obtained by previous workers in the case of dogs. According to this author a well marked characteristic of the pressure curve seen when the splanchnics are stimulated under good conditions in the cat, is that it rises rapidly for nine or ten seconds; then, without any check in the heart's rhythm, the curve is sharply cut down nearly to the level from which it came, whence it rises slowly again so long as the stimulus is continued. The drop, according to Elliott, is due to the liberation of adrenin into the blood, and he gives what seems to be very convincing evidence in favour of this view.

Anrep, who used dogs for his experiments, reports that stimulation of the splanchnic nerve causes a rise of blood-pressure which occurs in two phases. The second phase is accompanied by constriction of peripheral bloodvessels (even after denervation) and by acceleration and increased tone and augmentation of the heart (also after denervation). The secondary rise and all the concomitant phenomena are due to the discharge of adrenin into the circulation, and are absent after extirpation of both adrenal bodies. Every rise of blood-pressure, brought about by the agency of the nervous system, involves the co-operation of the chemical mechanism represented by the adrenal bodies. The constriction of bloodvessels in denervated limbs under splanchnic stimulation, which was regarded by Bayliss as a local reaction to increased pressure, is interpreted by Anrep as due to the action of adrenin. The rise of blood-pressure in asphyxia is also looked upon by this author as being partly due to constriction of somatic vessels as a result of the action of adrenin upon them.

Gley and Quinquaud have recently thrown doubt upon the validity of these experiments. They think that ligature of the vessels of the adrenal bodies or extirpation of the organs in the dog involves damage to some of the splanchnic vasoconstrictor fibres and that this accounts for the alteration in the splanchnic blood-pressure curve. In the cat and the rabbit, according to these authors, such alteration does not occur. In these animals the nerves are not so intimately connected with the adrenal bodies.

These criticisms on the part of Gley and Quinquaud

prompted Pearlman and myself to a re-investigation of the subject. We have performed a very large number of experiments upon dogs, cats and rabbits.

At the outset it was found that the conditions under which the experiment is performed makes a very considerable difference in the character of the curve obtained by splanchnic stimulation. There may also be differences characteristic of the different species and of different conditions of the animal. Anrep seems never to have obtained in his dogs under normal conditions a form of curve which we now look upon as the

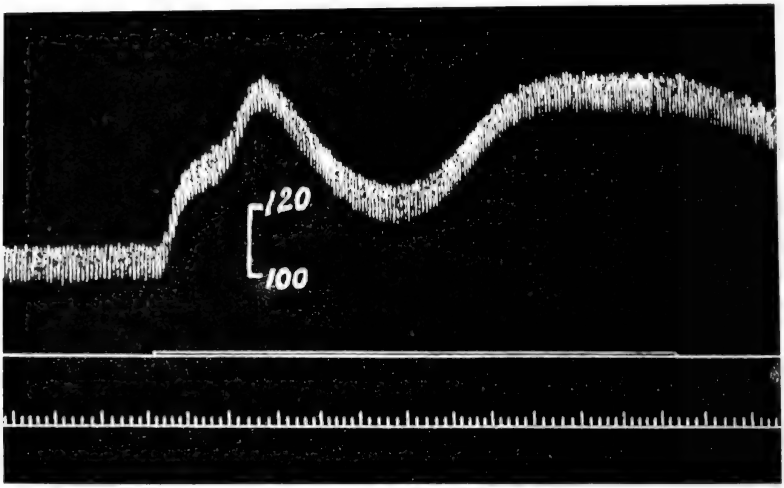


Fig. 47.—Dog, 12 K. Ether, vagi cut. Left splanchnic stimulated in thorax. Time tracing in seconds.

typical or normal, namely, a sharp rise (having a "hump" about half-way up) followed by a marked "dip" nearly down to the original level, and succeeded by a rise which lasts as long as stimulation is continued (see Fig. 47).

This occurs in dogs under ether with both vagi cut. Anrep used A.C.E. mixture and morphine. Chloroform, curare, and morphine sometimes modify the curve in such a way as to abolish the "dip," leaving only the "hump" on the rise (see Fig. 48).

In many of our tracings the "hump" and the subsequent "dip" are quite distinct (see Figs. 47, 48, 49) and the

augmentation of the heart is very manifest (47, 48, 49, and others).

The curve just described is, we believe, to be regarded as the normal effect of stimulation of the peripheral end of the splanchnic nerve in the dog, as well as in the cat and the rabbit, when these animals are under the influence of ether alone, or under morphine and curare in addition, although under the influence of the latter drugs the "dip" is much less pronounced and sometimes altogether abolished.

Anrep, in discussing Elliott's results, says "Eliott investigated the question in the cat, in which animal the 'step' becomes a distinct fall." As we have already stated, in our experiments there was no essential difference in this respect

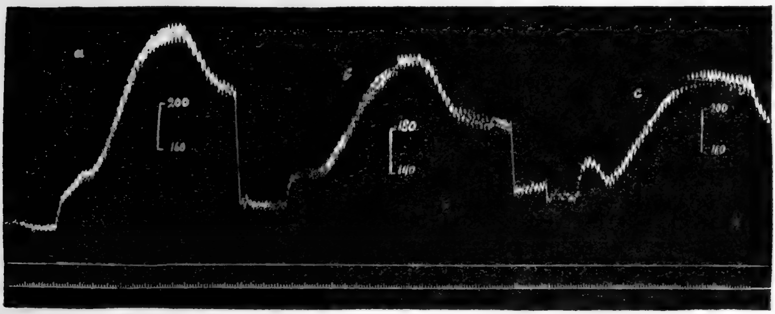


FIG. 48.—Dog, 10 K. Ether, vagi cut, both splanchnics cut in thorax. (*a*) Stimulation of left splanchnic five minutes after injection of 2 cc. of 1 % morphine sulphate. (*b*) Stimulation fifteen minutes later. (*c*) Stimulation fifteen minutes still later. The effect of the morphine wears off and the normal curve tends to appear again.

between dogs and cats. The "step" referred to by Anrep is therefore not what we have called the "hump," but something which occurs later and which we call the "dip." We have not been able to convince ourselves that the nature of the normal curve is dependent on nervous or emotional conditions either in dogs or in cats.

According to Elliott the "dip" of the splanchnic curve in cats does not occur if the adrenal bodies are excised or tied off. Anrep reports that the "step" in dogs is in a similar manner abolished by suppression of the adrenal bodies. Gley and Quinquaud, on the contrary, believe that there is an important difference in the results between dogs and cats. They state that interference with the adrenal bodies does not affect the

result in cats, and that it does so in dogs only because of a different anatomical arrangement. In their opinion, extirpation or ligature of the glands in dogs necessitates damage to nerve fibres, while in cats it may not.

According to our experiments there is no such difference

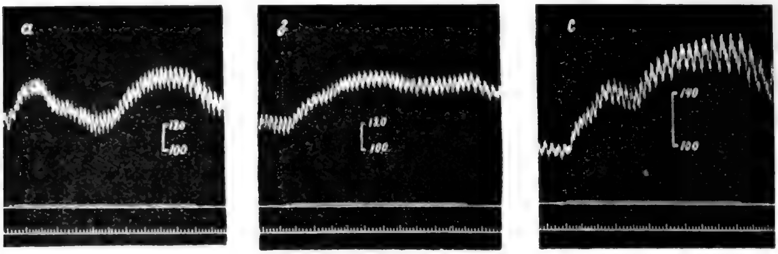


FIG. 49.—Dog, 10 K. Ether, vagi cut, both splanchnics cut in thorax. (*a*) Stimulation of left splanchnic. (*b*) Do. after clamping adrenal veins. (*c*) Do. after clamps have been released.

in the results obtained in dogs and cats, respectively. Our results, indeed, entirely confirm those of Elliott and apply equally to dogs, cats, and rabbits. We have usually obtained quite satisfactory positive results by simply clamping and unclamping the adrenal veins. Moreover, all necessary dissec-

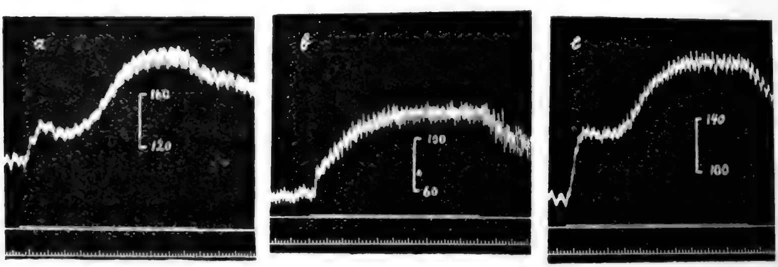


FIG. 50.—Bitch, 10 K. Ether, morphia, vagi cut, both splanchnics cut in thorax. (*a*) Left splanchnic stimulated. (*b*) Left splanchnic stimulated after left adrenal has been tied off. (*c*) Right splanchnic stimulated with right gland intact.

tion in the neighbourhood of the gland was carried out before the control experiment was performed (see Figs. 49, 50).

Fig. 51 shows that the results in the cat were similar to those obtained with the dog.

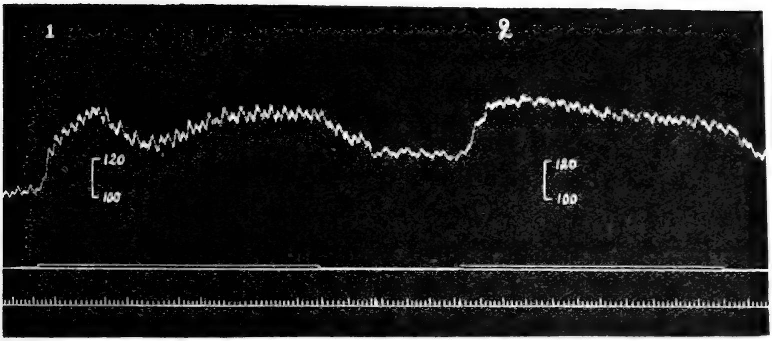


FIG. 51.—Cat, 2 K. Ether, vagi cut, both splanchnics cut in thorax. 1. Right splanchnic stimulated. 2. Right splanchnic stimulated after the adrenal veins had been clamped on the right side.

During the period of the first rise of blood-pressure under splanchnic stimulation there is marked passive dilation of the denervated limb. This is followed by pronounced constriction. In experiments on this subject we have always employed ether, morphine, and curare. When the adrenal veins are clamped or tied this constriction does not occur. Thus, our results are in accord with those of Anrep (see Figs. 52 and 53).

Anrep believes that the constriction of a denervated limb during the pressor response to stimulation of the central end of the sciatic nerve is due to the action of adrenin. He

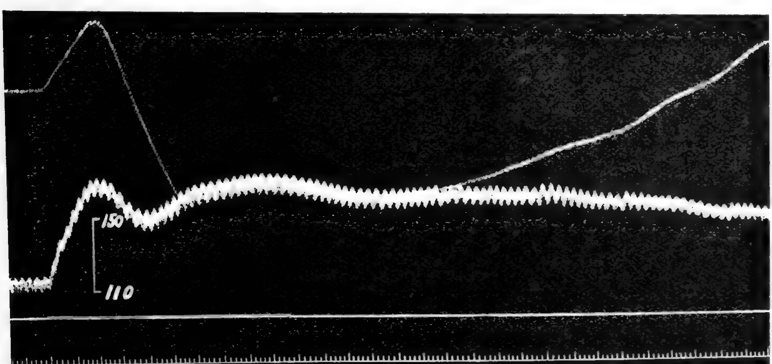


FIG. 52.—Dog, 16 K. Ether, morphine, curare, vagi cut. Upper curve, volume of denervated hind limb; lower curve, carotid blood-pressure. Time tracing in seconds. The right splanchnic was cut in the thorax and the peripheral end stimulated.

was led to this conclusion by the observation that after removal of the adrenal bodies from the circulation, the limb does not constrict, but follows passively the blood-pressure. Our own results enable us to confirm this observation (see Figs. 54 and 55).

Although suppression of adrenal function does not appear to affect the alteration in blood-pressure brought about by vasomotor reflexes, yet it seems exceedingly probable from the above

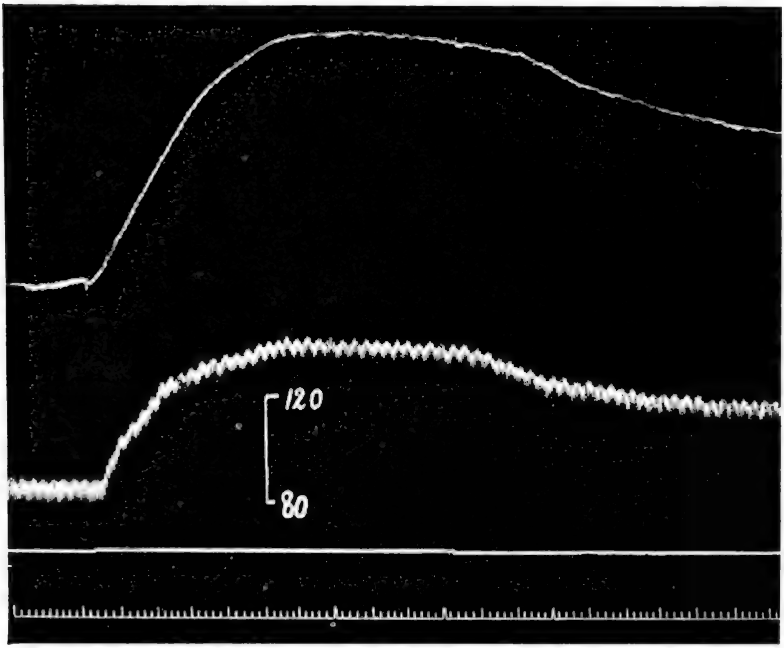


FIG. 53.—Same dog as in Fig. 52. In this tracing we see the effect of stimulating the right splanchnic after the adrenal veins had been clamped on both sides.

experimental results that, even when the limb is intact, the adrenals must play a considerable part in determining the distribution of blood in the body, when a stimulus is applied to an afferent nerve. It can scarcely be imagined that the presence of a nerve-supply can totally mask the action of the chemical agent. But it is difficult to be certain that the adrenal bodies play a part in vasomotor reactions in the normal state of the animal.

What follows after adrenal suppression when a weak stimulation causes a depressor response we have not ascertained.

If we investigate the difference between the intact and the denervated limb in regard to their respective responses to injection of smalldoses of adrenin (0·2 c.c. to 1 c.c. of a 1 :100,000 solution) we must bear in mind the results obtained by Hoskins,

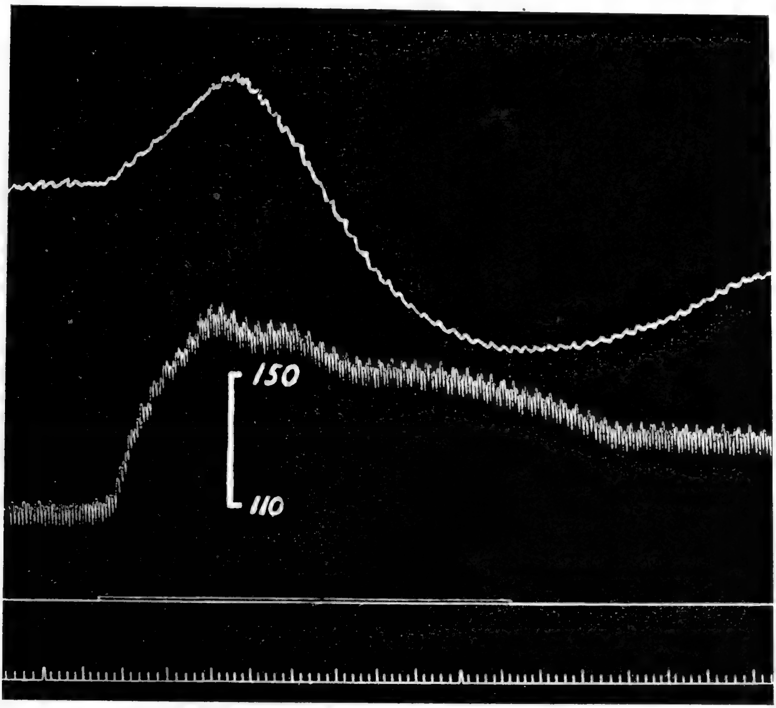


FIG. 54.—Dog, 10 K. Ether, morphine, curare, vagi cut. Upper curve, volume of denervated left hind limb. Lower curve, carotid blood-pressure. The abdominal cavity was open and the adrenal bodies had been cleaned in readiness for tying off. Stimulation of central end of right sciatic.

Gunning, and Berry. It was found that with nerves intact adrenin causes active dilatation of the muscles and vasoconstriction in the cutaneous vessels, so that while the entire limb usually constricts, a skinned limb will invariably dilate. This result we have been able to confirm. As further pointed out by Gruber, the results just described are obtained only when the nerves to the limb are intact. In the denervated limb, at

any rate within a certain period after the denervation, adrenin does not cause active vasodilatation in the muscles. These results agree well with what we find, namely, that when the splanchnic nerve is stimulated peripherally and the sciatic centrally in such a way as to give pressor responses, the intact limb follows passively the blood-pressure, while the denervated

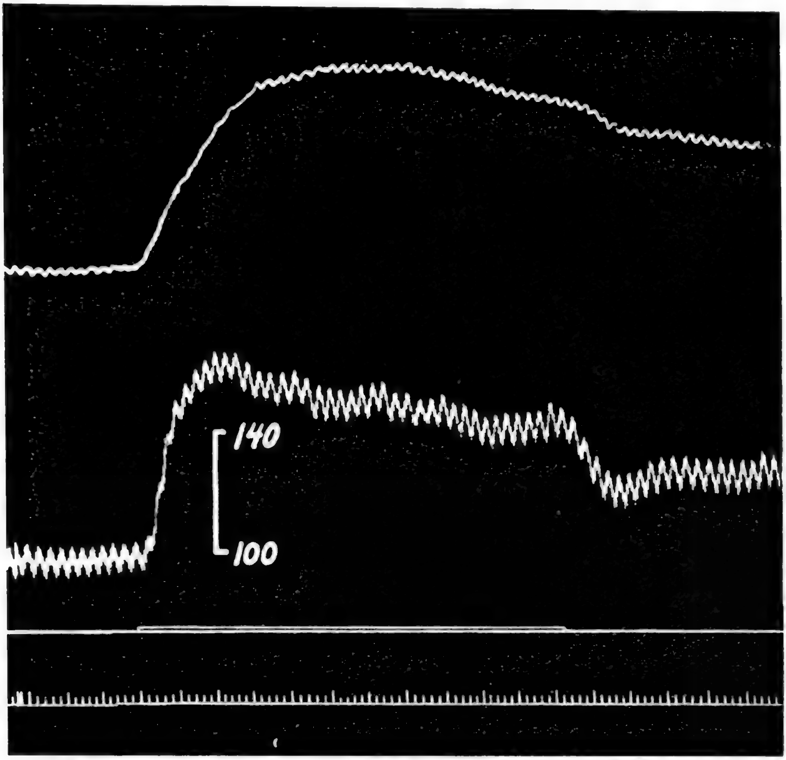


FIG. 55.—Same dog as in Fig. 54. The tracing is taken five minutes later than in Fig. 54, after the adrenals on both sides had been tied off. Stimulation of central end of right sciatic.

limb constricts. It is only reasonable to suppose that this is a natural consequence of the fact that in the denervated limb the muscles do not actively dilate, and therefore fail to produce the masking effect upon the skin constriction. We have been able to satisfy ourselves on these points by injection of adrenin as well as by stimulation of the nerves just referred to. This is, in our opinion, to be regarded as a provisional answer to the

query above, as to why the presence of intact nerves should interfere with the response to the chemical agent.

In regard to the effects of asphyxia, our results differ from those of Anrep. We have been unable to obtain tracings showing any significant difference in the behaviour of a denervated limb during asphyxia in an animal with adrenals suppressed as compared with one in a normal animal.

It seems impossible to avoid the conclusion that when powerful impulses are transmitted along certain afferent or efferent paths, the adrenal bodies (or, more correctly, the masses of chromaphil tissue contained within these bodies) play a part in the total response. Whether, under normal condition of the animal, the impulses which are so transmitted are sufficiently powerful to give rise to results similar to those of the laboratory experiments, or whether they are of such a character as to be adequate for such results, we cannot pretend to say. It is tempting to assume that the impulses may become adequate in physiological emergencies, as was suggested by Cannon and de la Paz.

It appears from our own tracings and from those of Elliott that, although the character of the splanchnic curve is seriously modified by elimination of the adrenals, the total rise of blood-pressure may not be affected, or may even be greater than before. It follows that in these cases the effect of the adrenin actually poured out into the circulation is a fall of blood-pressure and not a rise. This corresponds with the fact that small doses of adrenin produce a fall and not a rise. In other cases, however, the total rise is greater in the intact animal.

The question arises as to the nature of the process by which the adrenin is poured out into the circulation in sufficient quantity to produce, in laboratory experiments, the effects detailed above. It is generally assumed that the process is a true secretion, and that the splanchnic nerve is the channel along which the secretory fibres run. This is supposed to apply equally to experiments in which the splanchnic itself is stimulated and in those in which changes in the circulation are brought about reflexly by stimulation of different afferent nerves.

Some observers have alleged that the discharge of adrenin is the result of vaso-dilation of the adrenal body as a result of direct or reflex stimulation of its vaso-motor nerves. It would

appear very extraordinary if stimulation of the splanchnic caused vaso-dilation in the adrenal bodies, while it caused vaso-constriction in all the other abdominal viscera to which it sends fibres. Moreover, the experimental evidence on this point is not satisfactory. We might even go as far as to assume for the present that stimulation of the splanchnic constricts the vessels of the adrenal body. If this is the case, the constriction of the vessels of the gland might actually be the cause of the discharge of adrenin. For a certain amount of this substance contained in the veins and capillaries of the organ would be almost instantly driven out into the general circulation. This effect could, of course, be only of the briefest duration, though it might easily be sufficiently prolonged to produce the temporary effects above referred to. These effects, as we have seen, consist practically in a fall of the carotid blood-pressure and a constriction of vessels in certain somatic areas. This theory would account for the fact, observed by Elliott, that it is not possible to exhaust completely the gland by continued splanchnic stimulation. It would also explain the fact that the effects above detailed cannot be repeated until a certain time has elapsed since the first stimulation. If this were found to be the true explanation of what happens, we should then not have to deal with a true secretory activity of the glands, but only a mechanical expulsion of adrenin as a result of vaso-constriction.

In all such discussions it is important to bear in mind that the medulla of the adrenal body constitutes only a portion of the total chromaphil tissue in the body. In fact, it seems more than likely that there is more chromaphil tissue outside the adrenal bodies than within them. We can scarcely avoid this conclusion when we remember that the tissue in question is distributed widely in the sympathetic ganglia and in masses of various sizes throughout the abdomen.

This being so, it is remarkable that elimination of the adrenal medulla alone produces such marked and definite results as we have described. In the case of the effects of stimulation of the splanchnic nerve, it may be that the stimulation produces greater or more direct effects on the adrenal medulla than on such structures as the "abdominal chromaphil body," though the innervation of the latter would also be from the splanchnic. There is another possibility. Assuming that the glandular theory of adrenal activity is the true one, it might be urged

that the adrenal medulla is a chromaphil gland of a more highly developed type than that of the scattered masses of chromaphil cells in other regions.

Cramer has recently come to the conclusion that an increased activity of the thyroid gland leads to an increased liberation of adrenin from the adrenal bodies. He has formulated the conception that the thyroid and adrenal bodies form part of a mechanism for the chemical heat regulation of the body. He uses osmic acid vapour as a fixing agent to show the adrenin granules under varying conditions. The method has been applied to the adrenal bodies of mice and rats subjected to the conditions which were expected to produce alteration in the functional activity of the glands; these were thyroid feeding, thyroidectomy, injection of β-tetrahydronaphthylamine and other procedures. In all cases, he says, the method gave evidence of distinct changes in the medullary cells. There was evidence of the passage of adrenin granules into the blood-vessels of the medulla after injection of β-tetrahydronaphthylamine. The granules disappear if the glands are exhausted, and, in the various conditions demanding increased activity of the glands, fine black granules, similar to the granules of the medulla, appear in the cortex, especially in the layers of cells nearest the medulla. Cramer suggests that this is evidence that the cortex takes part in the functional activity of the medulla and that these two parts of the gland are not two physiologically independent organs.

These observations, if confirmed, have a very important bearing on the question of the relationship between cortex and medulla of the adrenal bodies. Up to the present time there has been no satisfactory evidence that the two portions of the gland have any relation to each other, either embryological or physiological.

Even if it could be shown conclusively that under certain conditions adrenin granules are found in the part of the cortex next to the medulla, this would by no means prove that the cortex normally takes a part in the production of adrenin. It might be supposed that under pathological conditions adrenin might not be able to escape by the usual channels, and so would overflow into the neighbouring cortex.

The histological evidence as to a secretory function of the adrenal medulla seems to us to be far from satisfactory.

A very interesting contribution to the subject of the internal secretion of the adrenal bodies has been made by Cannon and de la Paz. They point out that, according to the researches of Dreyer, Asher, and Tscheboksaroff, the adrenal secretion is under control of the thoracicolumbar autonomic (sympathetic) system. They further call attention to the fact that the phenomena of a major emotional exhibition in an animal indicate the dominance of sympathetic impulses. When, for example, a cat becomes frightened, the pupils dilate, the stomach and intestines are inhibited, the heart beats rapidly, the hairs of the back and tail stand erect—all signs of nervous discharges along sympathetic paths. The authors put to the test the suggestion that the adrenal glands share in the widespread subjugation of the viscera by sympathetic control.

The inhibition of contraction in strips of longitudinal intestinal muscle was used as a physiological test.[1] Blood was obtained from a cat when quiet, and again after the animal was excited by the presence of a barking dog. After an initial shortening the strip contracted rhythmically in blood from a quiet animal. In no instance did such blood produce inhibition. On the other hand, blood taken from animals after the emotional disturbance showed more or less promptly the typical relaxing effect. The effect was obtained in blood from the inferior vena cava near the liver. The authors believe that the effect was due to secretion on the part of the adrenal glands, and they offer a further suggestion that the persistence of the emotional state after the exciting object has disappeared may be in part due to an autogenous continuance of adrenal secretion.

A number of histological observations have been recorded, which have been interpreted as pointing to an active secretion on the part of the adrenal medulla. Manasse described brown masses in the bloodvessels of the adrenal body, and small highly refractive, colourless granules in the adrenal vein of the

[1] The authors discuss the various methods of testing for adrenin. The frog-eye method of Meltzer and Ehrmann did not give sufficiently striking results. Strips of ox artery, employed by Meyer, though highly sensitive, did not seem serviceable because of Schlayer's discovery that the method is less efficient when used with foreign blood. The uterus method requires several hours. So they finally decided upon the longitudinal intestinal muscle. One of the chief advantages of this preparation is that it responds by relaxing. This is very important, for other substances in blood than adrenin—*e.g.*, CO_2—will cause smooth muscle to contract, whereas known substances evoking relaxation of smooth muscle are few and unusual in blood.

dog, and others have found in blood taken from the adrenal vein a considerable number of highly refractive granules.

Carlier investigated the adrenal of a hedgehog, and described in the medullary cells deeply staining granules of varying size. These he found also in the lumina of the venous sinuses either singly or in clumps, and states that they could be observed in different stages of elimination from the cells. Stilling records that in "hunger" frogs the medullary cells are vacuolated, and take on the bichromate reaction in an irregular fashion. In summer frogs there is a distinct reduction in the amount of the medullary substance.

Hultgren and Anderson give a description of characteristic granules in the medullary cells and in the blood of the adrenal vein. They believe that they observed the passage of these through the endothelium of the bloodvessels. Some writers have described sharply defined spaces between the medullary cells, which are regarded as intercellular canals. These communicate with blood spaces, and sometimes it may be observed that not only the medullary vessels, but also the lacunæ and the intercellular spaces are filled with fine, darkly staining particles.

Ciaccio describes pericellular canaliculi, which he considers are intimately related to the processes of secretion, and specific granules in the medullary cells, which are of two kinds: the one having a special affinity for the salts of chromic acid—the chromaphil granules; the other having a special affinity for perchloride of iron.

Recently Stoerk and v. Haberer have stated that the characteristic granules of the protoplasm of the adrenal medulla are not cast out into the lumina of the vessels, but they represent structural units which are possibly to be regarded as the seats of chemical action whose products are to be looked upon as the true secretory materials of the medullary cells, which materials pass into the blood by some such process as diffusion. The fluid secretory product is the true bearer of the chromaphil reaction of the medullary cells, the granules having the reaction only in their secretory phase, when they are just forming the chromaphil substance. The fluid secretion can be recognized intracellularly (in both the protoplasm and the nucleus), and extracellularly (in admixture with the serum of the capillary and venous blood). Besides the typical fine gran-

ules of the medullary protoplasm there are coarse structures which occur on the side of the cells turned towards the vessels, and which reveal a different staining reaction from the granules. The capillaries are everywhere bounded by endothelium between the blood and the medullary cells.

Thus it would appear that the evidence physiological and histological that the adrenal medulla is, in fact, an internally secreting gland, and that adrenin is the product of its secretion is not very convincing. We have next to inquire whether adrenin acts directly upon the sympathetically innervated tissues, or whether it acts in some other more indirect or roundabout manner. Several writers believe that the function of the adrenal medulla is to render harmless the poisonous products of muscular activity, and render them serviceable for the regulation or the nourishment and innervation of the whole motor apparatus. Some are of the opinion that the waste products of muscular metabolism are, in fact, converted into adrenin. Thus the antitoxic theory is combined with that of internal secretion.

Notwithstanding the paucity of good evidence, clinicians and pathologists have now very generally adopted the internal secretion theory of the adrenal medulla, and the chromaphil or "hypertensive" system generally. Thus, Rolleston discusses the possible pathological relations of the internal secretion, and divides these into (1) Alteration in quantity—(*a*) absence, (*b*) diminution, and (*c*) excess; and (2) alteration in quality. There is no need to pursue this subject further.

2. *Theories as to the Function of the Adrenal Cortex*

We cannot at the present time allocate any definite function to the cortical portion of the adrenal body, though there can be little doubt that it exercises a very important influence upon the economy. The cortex is larger than the medulla, and is composed of epithelial cells, the appearance and microscopical structure of which suggests a high degree of secretory activity. Moreover, as we have seen (p. 152), there are strong reasons for thinking that the cortex is of more importance for the maintenance of life than the medulla.

The presence of fatty or fat-like substances in the cortical cells has been known for a long time, and has already been

referred to from the chemical standpoint (p. 203). They appear to have been first described by Ecker. The earlier observers referred to them definitely as fat droplets and fat granules. Kölliker calls attention to differences in the amount of the cortical fat in different classes of animals. The human being has a moderate amount.

Rabl investigated the micro-chemical reactions of the cortical cells in birds. He showed that the cortical granules are soluble in alcohol, ether, and chloroform, turn black with osmic acid, and red with alkanna. While, however, fat after treatment with osmic acid is insoluble in chloroform and oil of bergamot, the cortical granules are soluble in these reagents as well as in xylol. For this reason Rabl considers them only as "fat-like" bodies. These observations were found to be true also of the cortical granules of the horse and the dog. Alexander, however, noted that the cortical granules do not stain black with osmic acid, but only take on a brownish tinge; therefore, they must consist of some substance other than fat.

Kaiserling in 1895 reported that a large part of the granules in question are doubly refracting. Orgler concluded that the particles are not fat, but are related to myelin.

The granules are present in embryonic life, and, according to Plečnik, are not to be regarded as representing a fatty degeneration. In the medullary cells in the embryo there are granules which blacken with osmic acid, but these are not abundant, and at the fifth year granules are not present in all medullary cells. Now we find more and more cells which stain black with a clear centre, and after puberty these ring-shaped granules are alone present. After this time any solid granules in the cells show that they really belong to the cortex. Adrenal fat is different from other fat. In the external part of the cortex there are hollow spaces which are often lined with a layer of flat cells or ordinary cortical cells; these are best seen shortly before birth, and are absent in adults.

According to Bernard and Bigart, the cortex produces lecithin and pigment. It contains cells with compact (dark protoplasm, and cells with less compact (light) protoplasm, In the formation of the lecithin, fat-like droplets arise in the cells, and the process appears to progress from the periphery to the centre of the gland. In the pigment formation vacuoles

occur in the cells and become filled with fluid. This first occurs in the centre of the cells. Then the pigment appears in the form of granules at the border of the vacuolated part of the cells.

Labbé concluded that what Bernard and Bigart called "labile fat" is lecithin or a mixture of lecithins. He made an estimation, on the one hand, of the total fat by extraction with ether and alcohol, and, on the other hand the total quantity of phosphorus contained in the adrenal bodies, and found that the ratio of phosphorized fat to the total fat is 45·3 : 100 in the horse, 48·8 : 100 in the sheep, 52·7 : 100 in the rabbit. The phosphorized fat constitutes 6·77 per cent. of the organs in the horse; in man the ratio of the lecithin to the total fat is 13·1 : 100; the lecithin amounts to 2·08 per cent. of the total weight. The lipoids are increased after muscular labour.

Babes believes that the pigment of the zona reticularis arises from the lipochrome of the fatty layer. When the organ is very rich in fat, this is deposited in crystalline, doubly refracting structures resembling protagon in their reactions.

It is by no means clear that these lipoid (phosphorized fat) granules represent the actual secretion of the adrenal cortex. Nor, if such were the case, is it possible at the present time to suggest any reasonable theory as to their function.[1] (See, however, pp. 235–248.)

[1] Ciaccio claims that the lipoids in any tissue may be distinguished from the neutral fats by the following histological method: (1) Fixation for twenty-four to forty-eight hours in the following fluid:

Five per cent. pot. bichrom.	100 c.c.
Formalin	20 c.c.
Acetic acid	5 c.c.

(2) Five to eight days in potassium bichromate solution, 3 per cent. (3) Running water, twenty-four hours. (4) Alcohol, twenty-four hours. (5) Absolute alcohol, two hours. (6) Xylol. (7) Paraffin.

The sections are stained with a saturated solution of Sudan III. in 80 per cent. alcohol.

According to Ciaccio, the droplets in the tissues shown by this method consist of lecithin and other lipoids.

Bell has shown, however, that potassium chromate acts upon droplets of neutral fat in the tissues as well as upon the lipoids. It is certain that some lipoids, such as cholesterin, fatty acid mixtures, cerebroside, etc., are much more readily chromated than neutral fat. But the size of the droplet of neutral fat is a factor of great importance. A small droplet of triolein is com-

Mulon is of the opinion that in the adrenal cortex a complex lecithalbumin, elaborated by the activity of mitochondria, is poured into the blood-stream. This lecithalbumin he regards as the internal secretion of the adrenal cortex.

There are four views as to the function of the adrenal cortex :

1. That it is related to growth and development, especially of the sexual organs.

2. That it has an antitoxic function.

3. That it plays some part in the elaboration of the adrenin which is found in the medulla.

4. That the enormous development of the adrenal cortex in the human embryo is connected with the highly developed brain of man.

It is now tolerably certain that there is an intimate connection between sex characters and the adrenal cortex. Most of the evidence on this point is of a clinical nature.

Wooley and Bullock and Sequeira reported that tumours or hypertrophies of the adrenal body are sometimes associated with precocious development of the reproductive organs.

Glynn has given an excellent account of the tumours and rests of the adrenal cortex with their relationships to sex abnormalities. The following is a brief abstract of his classification :

A. Benign tumours. Cortical. Group 1. Diffuse hyperplasia passing into

Group 2. Adenomata, which may be bilateral. The cells contain a considerable amount of fat, and their arrangement is like that of the zona fasciculata.

B. Malignant tumours. Cortical. Group 1. Sarcomata : round-celled often lymphosarcoma, *i.e.*, small cells with an alveolar arrangement. These are common in children ; especially males between the ages of two and three.

Group 2. Hypernephroma or mesothelioma, a tumour having large polyhedral epithelial cells, recalling the structure of the adrenal cortex.

Hyperplasia of the adrenal gland or of accessory adrenals is frequently associated with pseudohermaphroditism. The great

pletely chromated in the same time that is required to chromate a large lipoid droplet. Ciaccio's technique is, however, a valuable method for the study of the fatty substances in the tissues, though it gives only a rough distinction between neutral fats and lipoids.

majority of these cases occur in female pseudohermaphrodites, that is to say, in females with internal organs of the male type, illustrating the *tendency of neoplasia or hyperplasia of the gland to be associated with the appearance of male characters in the female.* In most of the females the hermaphroditism was advanced, for prostates were present. Glynn quotes thirteen cases in illustration of this condition.

Adrenal hypernephromata are almost invariably characterized in children by precocious growth of the body generally and of the sexual organs in particular, with overgrowth of hair and fat. The skin becomes pigmented and the children are below the average in intellect. According to Guthrie, there are two types: (1) the obese type, met with in both sexes, but apart from the development of pubic hair the development of the sex organs is not exaggerated, though one of the females menstruated; (2) the muscular or "infant Hercules" type, occurring only in males, who may show true sexual precocity.

Hypernephromata of the adrenal body in children are much commoner in females than in males, and tend to increase the male primary and secondary sexual characters at the expense of the female.

Glynn quotes six examples of the tumour referred to in the last two paragraphs. These examples were found in young adult females and the growth was associated with changes in sex characters. It will be interesting to quote one of these:

A girl aged 16¾ years began to menstruate at 15, and continued to do so regularly for one year. When menstruation ceased she grew a beard and moustache, and hair developed also on the thorax and linea alba. The voice changed to the male type. She became very obese; the mammæ were well developed. She died of phlegmon of the hand. The external genitals were of the feminine type, the uterus measured 8 centimeters externally and was normal, but the ovaries were small and hard, showing no trace of ovulation, neither macroscopically nor microscopically. The right adrenal contained two yellow nodular tumours the size of a cherry, and the left was converted into a mass as big as a fist. Microscopically the right tumour consisted of round or polygonal epithelial cells in a network of capillaries; those in the left showed similar structure, but the meshes were wider and more irregular. A few larger cells, rich in chromatin and often multinucleated, were

also present. The condition is described as typical of "struma suprarenalis."

Gallais has recently observed and collected a number of cases in which tumours have given rise to striking abnormalities in the development of the reproductive organs. He groups them together under the title "genito-adrenal syndroma." One form of this syndrome is characterized by sexual precocity, other forms being such as are described above. He regards the cortex of the adrenal body as essentially a "puberty gland."

There are other evidences derived from comparative anatomy and physiology of the association between the adrenal cortex and the sexual functions.

Functional variations. Stilling, in his researches upon the adrenal body of the rabbit, observed periodic variations in the weight of these organs. There was enlargement of the glands in male rabbits during the breeding season. In the same communication he reports that the peripheral part of the cortex in the frog contains, during the summer, certain peculiar elements, the "summer cells," which atrophy later on during the pairing season. Patzelt and Kubik have, however, come to the conclusion that Stilling's summer cells are present the whole year round and are independent of age, sex, or state of nutrition. These authors prefer to call the cells in question acidophile cells from their staining reactions. A curious point is insisted upon by these writers. They find that the acidophile cells are only present in one species, viz., in R. esculenta. They are entirely wanting in the adrenal bodies of the other anura which they investigated, as also from the glands of the urodela and the reptilia. They note also that similar cells are found in the parathyroids of mammals and in the pituitary gland throughout vertebrates.

As far back as the year 1806 Meckel noted a relationship between the adrenal bodies and the reproductive organs.

Nagel in 1836 remarked that animals with large sexual organs and well-developed reproductive instincts possessed large adrenal bodies, which in birds and amphibians became still larger during the breeding season. Glynn remarks that it is highly probable that a similar change occurs in human beings, but that there are no recorded observations on this point. He suggests that such an enlargement, if it does take

place, may explain the curious tendency of any hair or "down" upon the face or body of a woman to increase in amount during pregnancy.

A hypertrophy of the adrenal bodies during pregnancy was noted by Guieysse in the guinea-pig, which enlargement chiefly affected the zona fasciculata.

It has been stated that removal of the ovaries results in hypertrophy of the adrenal cortex, especially the zona glomerulosa.

It has long been noticed that there is a resemblance between the cells of the adrenal cortex and the interstitial elements of the ovary and testis and those of the corpus luteum. Janosik looked upon all these cells as being very closely related. Podvissotzky insisted specially on the resemblance between the cells of the adrenal cortex and those of the corpus luteum. This was further emphasized by Mulon who, from observations on guinea-pigs, goes so far as to speak of the corpus luteum of pregnancy as a temporary cortical adrenal body.

It seems hopeless at present to attempt any explanation of the precise manner or the essential mechanism of the influence of the adrenal cortex upon the reproductive organs. It is perhaps most in accordance with current views to admit the hypothesis that a certain hormone, or certain hormones are secreted by the adrenal cortex which are passed into the blood-stream and so reach and exert their action upon the reproductive organs. It has been suggested that the adrenal body may act through the mediation of the pituitary, but so far as I am aware, no changes in the latter organ have been observed in any of the cases referred to above.

Much has been written and many hypotheses have been put forward on the subject of the relationships between the various organs furnishing an internal secretion. Much of this is purely hypothetical, and a great deal remains to be discovered before we can formulate any general statements. (See p. 395.)

It is possible that the simpler physiological conception of underaction or overaction respectively of the various ductless glands, now used to account for the various pathological states, may have to be supplemented or superseded by a consideration of modified or deranged function.

Recently an attempt has been made to investigate the relations between the adrenal bodies and the reproductive

organs by studying the effects of feeding animals with the adrenal bodies or preparation made from them.

Some years ago the present writer failed to observe any immediate physiological effect upon dogs, cats, and rabbits, after feeding with the adrenal bodies of sheep; just as the administration of large doses of extracts (in some cases made from the medulla only) failed to produce any noticeable rise in the blood-pressure in the human subject. D'Amato has also shown that very large doses do not increase pressure, although they may cause arterial degeneration. As we have seen above, Leyton states that adrenal extract although it ordinarily fails to produce elevation of blood-pressure when administered by the mouth, will bring about this effect in cases of Addison's disease.

But the experiments about to be described are of a different character. They involve the administration of comparatively small doses of gland substances over a long period, in order to test the effect upon the growth of the body as a whole, and the reproductive organs in particular. R. G. and A. D. Hoskins have carried out a series of experiments on white rats in which certain of the young animals were fed with desiccated adrenal gland [1] while certain others were kept as controls. Forty-five rats were fed with adrenal body for varying periods of from two to nine weeks. Twenty-six animals from the same litters were kept as controls. The rate of growth and the weights of various glands were determined in each series. No differences between the two series could be detected in the case of the kidneys, heart, pituitary body, thyroid, thymus or adrenal bodies. The spleens of the experimental series were somewhat smaller than those of the controls, but highly variable in size. The ovaries in the few cases studied were larger in the experimental series. The testes (twenty-six experimental, thirteen control) showed hypertrophy. These results are in confirmation of the clinical evidence above stated, and indicate that the adrenal bodies exercise a stimulating effect on thé growth of the testes in young animals.

The authors of the communication just referred to discuss the question as to what constituent of the gland the testicular hypertrophy is due to. They conclude that it is in all probability to be ascribed to the cortical portion. But it is

[1] Parke, Davis & Co.

obvious that the experiments would be more satisfactory as regards this point if the cortex only were employed for the feeding. A further criticism of the experiments above described seems justified from the fact that desiccated gland was used. I believe that the material is "degreased" before it is "desiccated," and the former process would be likely to remove many "lipoids," some of which might be among the physiologically active substances. In future experiments, therefore, it would be well to use fresh cortex only, in order to eliminate these sources of error.

It has been stated that the injection of adrenal cortex in white rats causes falling out of hair and some changes in the ductless glands.

Linser has recorded the case of a giant with a huge adrenal growth, and Scudder has put forward some evidence to show that malignant growths of the cortex tend to produce metastases in bone.

2. The theory that the cortex has the power of neutralizing toxic substances has presented itself in two principal forms: (*a*) That the gland destroys the poisonous products of body metabolism, especially those arising from muscular activity. This is the theory of auto-intoxication, put forward by Abelous and Langlois, and was originally applied to the whole gland before the active principle of the medullary chromaphil tissue was discovered. But a modification of the view is now held by Boruttau and Langlois to apply to the secretion of adrenin by the chromaphil cells. (*b*) That the cortex has the duty of destroying poisons which come from without the body. That the cortex may exert antidotal properties is suggested by Myers' observation that cobra poison, after being mixed with an emulsion of the adrenal cortex, was no longer toxic, control experiments with emulsions of the medulla and of other organs giving negative results. Experimental infections with various organisms, such as the tubercle bacillus, and with toxins, such as the diphtheria toxin, give rise to hypertrophy of the cortex, and in some instances apparently to deficiency of the medulla. Ritchie and Bruce report in diphtheritic toxæmia in guinea-pigs exhaustion of all adrenin from the adrenal medulla.

3. It has often been suggested that in the cortical cells the material which is to furnish the active agent of the medullary secretion—the adrenin—passes through the initial stages of

formation, and that the process of elaboration is completed in the medulla. This view has been tentatively proposed by Schäfer and Herring, and more definitely formulated by Abelous, Soulié, and Toujan. These authors believe that the active principle can be obtained in small quantities from the cortex, where it is manufactured from tryptophane. It is then passed into the medulla and stored there. These views have not received support, and the experimental evidence in their favour is not convincing.

Elliott and Tuckett have made an attempt to solve the problem of a possible functional relationship between cortex and medulla. Among mammals the guinea-pig is conspicuous by the huge development of its adrenal bodies, the growth being chiefly of cortex. They point out also that the lower the animal is in the scale of vertebrates the larger is its stock of chromaphil tissue. Gestation accelerates the growth of the gland.

As signs of secretory activity Elliott and Tuckett recognize four substances in the glands :

(1) A fatty substance.
(2) A doubly refracting substance.
(3) Brown granules of the cortex.
(4) The chromaphil substance of the medulla.

The first two are nearly related ; the doubly refracting substance increases with rest, when the fat becomes less abundant. In phases of " exhaustion " the doubly refracting substance vanishes and the fat spreads over all the cortex. But neither are essential factors in a generalized type of cortical activity, for neither appears in the sheep. The brown granules occur characteristically and plentifully in the guinea-pig, and over a restricted area in the ornithorhyncus. They accumulate with rest, and disappear very early in exhaustion ; the cytoplasm of the cells in which they have been stored then develops fat. Exhaustion of the medulla is shown by a progressive thinning of its yellow stain with potassium bichromate. In states of extreme exhaustion this stain finally vanishes.

The only indication found by Elliott and Tuckett of any functional relationship between cortex and medulla is the observation that the changes described above, both in cortex

and medulla, move in close parallelism with one another in pathological states of the body. On the other hand, stimulation of the splanchnic nerves seems to affect chiefly the medulla (see p. 224 *et seq.*).

4. The enormous development of the adrenal cortex in the human embryo is possibly connected with the highly developed brain of man. Alexander has suggested, and Kohn supports the suggestion, that the connection may depend upon a lecithin product in the adrenal cortex in accordance with the lecithin requirements of the growing brain.

It must be confessed that both as to the function of the cortex and as to a possible relationship between it and the medulla, we are still almost entirely in the dark.

8. Summary of Views as to the Probable Functions of the Adrenal Bodies

As we have seen above, it is difficult to adduce any satisfactory evidence that the secretion of the chromaphil tissue is of any use whatever in the normal state of the animal.

We have also seen that the suggestion has been made that the secretion is of great service in certain emergencies. Certain experiments seem to show that during times of emotional stress the adrenal bodies pour into the blood sufficient adrenin to be of some service, possibly in increasing the power of sustained muscular activity. This view has received very general approval, but it would be rash to affirm that it has been firmly established. Stewart and Rogoff conclude that fright has nothing to do with the results.

The experiments of Hoskins and McClure, taken in conjunction with others above referred to, furnish sufficient evidence to warrant us abandoning the tonus theory of adrenal secretion. But the theory is still put forward by writers on clinical subjects, and is made to account for the low blood-pressure in Addison's disease. The fact is that we have not a single physiological observation (except perhaps the effect of adrenin on the contraction of skeletal muscles) which throws any light on the pathology of Addison's disease.

The following is a brief summary of what, in the opinion of the present writer, represents the state of our knowledge concerning the adrenal bodies.

1. What we call the adrenal body represents the anatomical association of two elements, each one of which is derived from a separate and independent system. The adrenal body proper or cortex is part of the "cortical" or "inter-renal" system. The medulla is simply an accumulation of chromaphil cells of the same nature, histologically, chemically, and pharmacodynamically, as similar but smaller masses along the sympathetic at other levels.

2. There is no clear evidence that these two systems are functionally related to one another.

3. The adrenal medulla (as well as the "chromaphil tissue" generally) is derived from the sympathetic nervous system, and is alleged to facilitate this system's functions in certain physiological emergencies.

4. The cortex is derived from the germ epithelium and there is considerable evidence that it has important functions in connection with the development of the reproductive organs.

5. There is a considerable mass of clinical evidence that tumours of the adrenal cortex are frequently associated with sex abnormalities.[1]

6. Additional evidence in the same direction is furnished by the enlargement of the cortex during breeding and pregnancy.

7. It is possible that a final solution of the problem as to the relation between the adrenal gland and sex will only be arrived at when the wider problem of the relationships between the various ductless glands shall have been solved.

8. Feeding young animals with adrenal gland substance seems to stimulate the growth of the testis.

9. Inanition produces marked hypertrophy of the adrenal bodies (McCarrison, Vincent and Hollenberg).

10. The cortex is the part of the gland which is essential to life. We do not know why its removal causes death, but it is possible that this is due to some defect in muscular metabolism.

[1] The association is frequent, though not constant.

CHAPTER XII

THE CAROTID AND COCCYGEAL BODIES

A. The Carotid Body

Historical

THE carotid body has been known for a very long time. Neubauer described and depicted the body in the year 1786, and Haller had mentioned it many years previously. Andersch was the first to call the body the "gangliolum intercaroticum." In the nineteenth century, Mayer rediscovered the body and showed that it is an organ of constant occurrence.

It was Luschka who substituted the name "glandula carotica" for Andersch's "gangliolum intercaroticum," and thereby initiated a controversy which has lasted up to the present time. He was struck with the difference between the "ganglion intercaroticum" and the other ganglia of the sympathetic. A careful examination convinced him that the structure was not a ganglion, but a gland made up of cell columns and vesicles. He could find only a few nerve cells in the body.

The glandular tubes and vesicles described by Luschka were regarded by Arnold as ramifying branches of the artery which supplies the body, while the epithelial cells are those of the lining wall of the bloodvessels. This author proposed the name "glomeruli arteriosi intercarotici."

Eberth places the carotid body side by side with the coccygeal ("plexus vasculosus coccygeus") as the "plexus arteriosus caroticus," and this view was adopted by anatomists generally.

Katschenko investigated the development of the carotid body in the pig, and reported that it is not of epithelial origin. It is formed in the outer coat of the carotid artery, and is intimately related to the neighbouring nervous ganglia.

Marchand describes the development of the carotid body

in the human subject. He suggests the name "nodulus caroticus," and considers the body in question to be a rudimentary organ.

Stilling made the important discovery that the carotid body contains some cells which stain brown with potassium bichromate. This observation was confirmed by Kohn, who has added to the long list of names attached to this tiny body, by suggesting that it be called the "paraganglion intercaroticum."

Comparative Anatomy and Embryology

In the human subject the carotid glands are small bodies situated just above the bifurcation of the common carotid artery on each side, and between its internal and external branches. According to Luschka, the gland is of an elongated spherical shape, 5 to 7 millimetres long, 4 to $2\frac{1}{2}$ millimetres broad, and $1\frac{1}{2}$ millimetres thick. Sometimes it is divided into two or more nodules. The body is greyish or brownish-red in colour. Its consistence is more compact than that of a nerve ganglion, and its substance cannot be easily teased out with needles.

In all, or in nearly all mammals so far investigated, the carotid body has been found in the neighbourhood of the bifurcation of the common carotid artery, either exactly at the bifurcation or somewhat higher up in the connective tissue between the internal and external carotid arteries. Both these and the common carotid may give twigs to the body.

Many observers have noted the richness of the nerve-supply to the carotid body; this supply is mostly from the sympathetic nervous system. According to Luschka, there is situated between the internal and the external carotid arteries a rich nervous plexus beset with tiny ganglia—plexus intercaroticus—which is a complex of fibres from the superior laryngeal and the glosso-pharyngeal nerves, and a variable number of twigs from the superior cervical ganglion. According to Svitzer, there are twigs to the body from the superior cervical ganglion, from the nervi molles Halleri, from the trunk and the pharyngeal branch of the vagus, from the superior laryngeal branch of the vagus, from the hypoglossal, and from the sympathetic above and below the superior cervical ganglion.

According to Maurer, the body is absent in fishes, but present in Amphibians and all higher vertebrates. In the Anura an

epithelial bud occurs in the region of the second gill-cleft, which at first resembles the parathyroids from clefts 3 and 4, but soon becomes distinguished by its relation to the branchial arteries. Zimmerman states that there are no epithelial elements, but only a proliferation of the vascular wall. Maurer believes that the carotid body of Rana is homologous with the carotid body of higher vertebrates. The matter is doubtful in reptiles and birds, though Maurer believes that in Echidna the origin of the structure is the same as in the frog. Schaper, however, believes that in mammals the body is a development of the wall of the artery. Maurer acknowledged that our knowledge of the development is still very imperfect, and suggests that under a single name several different structures have been described. Kohn believes that the carotid body is derived from the embryonic ganglion cells of the sympathetic plexus.

Microscopical Structure

According to Kohn, there are four principal types of the organ according to the arrangements of the cellular elements. In the first type the body is compact and circumscribed. The connective tissue is so finely divided that the cellular character of the tissue is predominant. The carotid gland of the cat is a good example of this type. (See Fig. 56.)

In other cases the connective tissue is distributed into the gland in larger amount, and so two new types arise. In one of these the organ has a kidney-like form. At the hilus there is a considerable accumulation of connective tissue with blood-vessels and nerves. From this region radial septa run into the interior, which divide up the organ into lobules after the manner of a secreting gland. The lobular formation is found typically in the carotid gland of the monkey (*Macacus rhesus*). In man the gland is divided by its connective tissue into small separate islets.

The fourth type is exemplified in the carotid body of the rabbit, which consists of scattered islets and strands of cellular tissue. This may be called the diffuse type (Kohn).

The cells are of variable, for the most part of considerable, size. Their form is manifold; they may be prismatic or cylindrical, but they are frequently flat. Kohn does not deny that there is a certain resemblance to an epithelial structure,

though he is opposed to the view that the chromaphil tissues are of a secretory nature.

The cell body is finely and uniformly granular. The nucleus is large, granular, and shows a distinct nuclear membrane and nucleoli. As a rule there is one nucleus, but there may be two. In some cells the nucleus is so poor in chromatin that the cell resembles a nerve cell. Many cells, moreover, possess a cell membrane.

According to Kohn all the true specific cells of the body are chromaphil cells—that is to say, they become stained of a yellowish or brownish tinge by solutions containing bichromate of potassium. Kohn states that the degree of coloration varies within very wide limits. The cells are arranged in groups, and the body is permeated by non-medullated nerve fibres and scattered nerve cells.

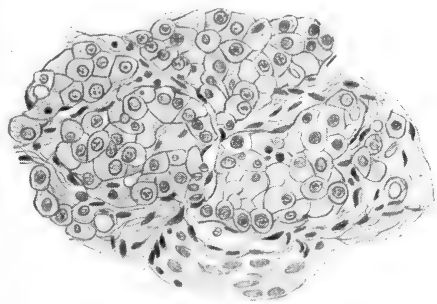


FIG. 56.—Portion of a section through the carotid body of a cat. (Drawn by Mrs. Thompson.)

The organ is richly provided with blood-vessels. The arteries break up into a close capillary network, which penetrates the cell groups, and where the amount of connective tissue is small, come into close contact with the cells.

Kohn lays great stress upon the intimate relation existing between the nerve fibres in the body and the specific carotid cells.

The carotid body is developed from the embryonic ganglion cells of the intercarotid sympathetic plexus.

From the foregoing account it would seem that we are justified in including the carotid body in the category of the chromaphil tissues. The body, then, has no special functions, other than those of the chromaphil tissues generally, and all that has been said on the pharmacodynamical effects of adrenin, the chemistry of adrenin, and the functions of the adrenal medulla, applies in all probability to the carotid body.

B. The Coccygeal Body

The coccygeal body in the human subject is a small organ, at most 2·5 millimetres in diameter, sometimes broken up into a number of smaller bodies, placed immediately in front of the apex of the coccyx, and receiving branches of the middle sacral artery.

The body was discovered by Luschka in 1860, and since that date various opinions have been held in regard to its structural elements and its essential nature. These opinions have been classified by Schumacher as follows:

1. The cells of the body are not constituents of the vessel walls, but thread-like accumulations of specific cells, into which bloodvessels penetrate.

2. The cells are constituents of the bloodvessel walls:

(*a*) They are derived from the endothelium.

(*b*) They are derived from the adventitia ("perithelium" cells).

(*c*) The cells are related to those of the middle coat of the middle sacral artery and its branches.

Schumacher has given a full description of the "glomus coccygeum" in the human subject, and the "glomeruli caudales" of other mammals. According to this author, the former corresponds in all essential points to the latter, the only difference being that the "glomeruli caudales" of animals consist of several detached portions corresponding to the caudal segments, while the "glomus" of man is represented by a principal structure at the tip of the coccyx and some smaller nodules.

It has been shown by Stoerk that the cells of the coccygeal body do not give the chromic reaction at any period of life, and that they bear no histogenetic relation to the sympathetic nervous system.

The "glomeruli caudales" and the "glomus coccygeum" appear to be arterio-venous anastomoses (Schumacher), and the epithelioid cells are transformations of the smooth muscle fibres of the middle coat of the artery.

The structures in question are probably to be regarded as safety-valves in the course of the peripheral circulation. The balance of evidence is against their having any kind of internal secretion.

CHAPTER XIII

THE FUNCTIONS OF THE THYROID AND PARATHYROIDS

A. Introductory: The Organs derived from the Region of the Pharynx and Gill-Clefts

THE organs in question may be divided into two groups. The first group is represented by structures which arise simultaneously with the gills and gill-clefts—viz., the thyroid, the thymus, and the post-branchial bodies (the suprapericardial bodies of v. Bemmelen). The organs of the second group are developed concomitantly with the degeneration of the gills and the closing of the clefts, from whose epithelium they arise. These are the " branchial bodies " of the Anura and the parathyroids throughout Amniota.

B. The Comparative Anatomy and Histology of the Thyroid and Parathyroid Bodies

Cephalochorda and Cyclostomata

1. In Amphioxus and Ammocœtes the thyroid is a sausage-shaped glandular body which branches in a fork-like manner and retains its opening into the pharynx. This indicates a relationship to the hypobranchial furrow or endostyle of Tunicates. The epithelium lining this saccular gland is ciliated, and secretes mucus.

In Petromyzon the connection with the pharynx is broken, and the gland consists of a number of closed vesicles lined by tall columnar epithelium, and containing a colloid substance in their interior.

The details of the metamorphosis of the endostyle in Petromyzon have been recently worked out by Marine. The endostyle persists throughout the larval period in full activity. Then, at the metamorphosis, it undergoes involution, all but a remnant disappearing. This remnant assumes the form of the

ductless thyroid, and persists throughout life. The endostyle in Amphioxus and Ammocœtes appears to be a gland which secretes a slime of service in the collection and possibly in the digestion of the food.

2. Simon found the thyroid in all classes of Fishes. In **Elasmobranchs** the thyroid is a moderately large compact organ situated at the anterior end of the ventral aorta, in front of the bifurcation of the branchial artery. The gland is yellowish-white in colour, and the anterior extremity is elongated and prolonged to a point in some species. In other species the thyroid is nearer the end of the tongue, situated on the coraco-hyoid muscles, immediately under the coraco-mandibular, and may be spheroidal, flat, or irregular in shape. Groups of follicles are sometimes detached, forming accessory thyroids.

There is a striking uniformity in the general microscopic appearance of the thyroid gland throughout all vertebrates above the Cyclostomata, and the thyroid of the Elasmobranch fishes would be immediately recognized as such by any student who had once seen under the microscope a preparation made from the mammalian thyroid. Such differences as are found throughout vertebrates, in regard to the amount of intervesicular connective tissue, intervesicular epithelial tissue, size of the vesicles, and so on, are equally to be recognized among the glands of Elasmobranchs themselves.

Perhaps the most interesting of the species examined is *Scyllium canicula.* In this fish the thyroid contains not only the usual vesicles, but also several bodies composed of two kinds of cell—lymphoid and epithelial. Since parathyroids have not been described by the embryologist, these bodies are probably nodules of thymus.

Throughout Elasmobranchs the shape of the cells lining the vesicles varies extremely in different species. Thus, in some it is of a tall columnar, and in others of a low cubical, form. The colloid contents appear to be of the same character as in other vertebrates.

3. Among **Teleostean** fishes McKenzie gave an account of the anatomy of the thyroid in *Amiurus.* The gland is placed beneath the copulæ of the branchial arches and surrounds the anterior end of the branchial artery. It is an unpaired structure extending in the median line from the origin of the vessels at the first pair of gill arches to a short distance behind the origin

of the single stem for the third and fourth pair of arches. Although richly supplied with blood, it appears of a whitish colour contrasted with the bloodvessels among which it lies. The framework of the organ consists of loose connective tissue which does not form a lining membrane, but simply passes over into the like tissue sheathing the adjacent parts and the vessel which it surrounds. The usual vesicles of the thyroid are scattered throughout this connective tissue, showing a tendency to arrange themselves in short rows. The wall of the vesicle consists of a single layer of columnar epithelium resting on a basement membrane formed from the surrounding connective tissue. The epithelium is readily made out in the young fish, but disappears frequently in the adult.

On re-examining *Amiurus* it was found that the connective tissue in which the vesicles lie is very compact and not loose, as described by McKenzie. Further, in none of the slides was the epithelium columnar, and the statement that the cells of the vesicles rest upon a basement membrane could not be verified. In an embryo specimen the vesicles were filled not with colloid, but with some material full of nuclei [epithelium or adenoid tissue (?)].

The thyroid of Teleostean fishes is of special interest owing to the fact that goitre (active thyroid hyperplasia) is not uncommon (Marine and Lenhart, Gudernatsch), and is stated to become carcinomatous. The tendency of the growth to spread seems to be connected with the fact that the gland is not circumscribed, has no capsule, and so the gland follicles are distributed over a wide area, and outstanding groups of cells may become fresh foci of tumour formation.

No parathyroids have been found in fishes, but the post-branchial body is developed.

4. In the **Urodela** the thyroid occupies a more superficial position than in the Anura. The development has been worked out in Triton, Siredon, and Necturus. The gland arises from a median rudiment, and subsequently becomes paired.

In *Sperlerpes ruber* the vesicles are approximately of the same size as in the frog. They do not number more than a dozen. There is less connective tissue than in the frog, and the vesicles are therefore more closely packed together. The colloid contents are of the same character as in vertebrates

generally. The gland is distinctly more vascular than in the frog.

In Triton there appear to be two, or even three, parathyroids developed on either side. In Sperlerpes there is sometimes only one. The general histological features appear somewhat different from those of the corresponding structure in the frog. The body is of extremely small dimensions, but contains fairly large blood capillaries. It is encapsuled, but its constituent cells do not possess the whorl arrangement so characteristic of the parathyroids of the frog.

The post-branchial body occupies a corresponding position to that in the frog; it consists of about eight vesicles. These have a taller epithelium than the thyroid vesicles and contain colloid.

5. In the **Anura** (*a*) the thyroid has been most carefully studied in the frog. In this animal the gland of each side is an oval corpuscle placed ventrally to the root of the processus postero-medialis of the hyoid cartilage, and occupies a deep concealed position. It is very difficult, as a rule, to find by ordinary dissection.

Like the thyroid of all animals, that of the frog consists of a number of closed vesicles, the walls of which are composed of a single layer of epithelial cells. The cells lining the vesicles are cubical, but small, corresponding with the small size of the vesicle and of the whole gland. The intervesicular tissue, instead of being cellular as in mammals, is formed of fibrous connective tissue with scattered nuclei and bloodvessels. The colloid contents of the vesicles call for no special notice.

(*b*) Accessory thyroids are not uncommon in the frog; they have the same structure as the main thyroid.

(*c*) Parathyroids in the frog are first mentioned by Ecker, who considered them as representatives of the thymus, and by Leydig, who considered them, together with the "ventral branchial body," as representing the thyroid. That they are very different from the thyroid in their structure Leydig himself stated. The suggestion that one of the bodies described by Leydig was the ventral branchial body and the other the parathyroid is made by Gaupp, and on referring to Leydig's monograph and looking at his plates, it seems clear that this is the case. After the work of Toldt, the bodies were called for some years "Nebenschilddrüsen," a term which

has naturally led to much confusion, owing to the fact that the same term has been sometimes applied to the true accessory thyroids. The matter was finally made clear by Maurer, who recognized the homology of these organs with the glandulæ parathyroideæ which were discovered in higher animals by Sandström in 1880, and independently by Baber, Horsley, and Gley.

The parathyroids of the frog are represented on either side of the body by two oval or spheroidal corpuscles placed one behind the other at the side of the jugular vein in the sinus sternalis. They are sometimes quite close to the ventral branchial body, and sometimes at some distance from it; they are greyish-red or yellowish in colour, and in adult specimens of *Rana esculenta* may reach 1 millimetre in diameter.

The arteries to the corpuscles come from the musculo-glandular branch of the external carotid. The veins pass into the external jugular.

There may be more than two glandules on either side.

The parathyroid has a tough, fibrous capsule, and the interior of the body is compact. There are closely placed elliptical or spindle-shaped nuclei which stain deeply. The cells are longish, and so disposed that they describe spiral turns. The cell outlines of the glandules are distinct even when viewed under a low power of the microscope. Some of the nuclei are rounded, while others are distinctly elongated. Some of the cells are vacuolated, probably owing to the removal of fat droplets in the process of preparation for microscopical examination. In some sections the disposition of the more central part of the organ is such as would be found if the body had been subjected to a process of torsion. The cells vary very considerably in shape; they may be oval, cubical, pentagonal, spheroidal, or elongated.

(*d*) The post-branchial body is of considerable importance in any discussion of the development of the thyroid body. Its relationship to the latter body in higher vertebrates will be fully discussed later (p. 261). De Meuron was the first to discover the structure in the frog and in the toad, and to work out its development. He considered that it is homologous with the suprapericardial body which had been described by v. Bemmelen in Elasmobranchs. Maurer has supported this view, and introduced the name "post-branchial body" to

express its relation to the gill-clefts. V. Bemmelen looked upon his suprapericardial bodies as homologous with gill-clefts, but Maurer considers them to be of a different nature, because in all vertebrate animals in which they occur they arise immediately behind the last gill-cleft, whether this be the fourth, fifth, or sixth.

The post-branchial body has so far been discovered in all Gnathostomata, but in many forms it appears only on one side.

The post-branchial body of the frog is a tiny structure which lies at the side of the aditus laryngis under the epithelium of the floor of the pharynx. It consists of three or four small vesicles lined with cylindrical epithelium. Maurer states that these cells sometimes carry cilia. The vesicles contain a coagulated albuminous substance and debris, but no colloid.

6. In **Reptilia** the thyroid is unpaired in some families (Ophidia and Chelonia), while in the Lacertilia the organ is bilobed in young specimens, paired in older ones. The organ lies immediately in front of the pericardium. The parathyroids and post-branchial bodies are intimately united, paired, and placed anteriorly to the thyroid. Their precise anatomy differs in different groups. The thyroid gland presents no special features so far as microscopical structure is concerned.

In *Chrysemys picta* and *Pseudemys scripta* the parathyroid contains vesicles, and in the latter species some of these vesicles contain colloid.

In *C. picta* the post-branchial body also contains colloid, but the parathyroid and post-branchial body are very considerably confused together in this and some other species.

In *Testudo græca* there exists on each side an "inferior internal" parathyroid, applied to the carotid ("glandule parathyroïdienne"), and a "superior external" parathyroid included within the substance of the thymus ("glandule parathymique"). These bodies are about 1 millimetre in size, round, oval, or triangular, and possess processes which may be as long as the organ itself. The glandule which is embedded in the thymus is particularly rich in such processes (Aimé).

7. In **Aves** the general features of the thyroid are the same as in reptiles. The adult gland is a paired organ placed near to the large vessels of the neck. The vesicles are frequently small and irregular in outline. The intervesicular

tissue is large in amount, and in certain regions and in certain specimens forms large areas of solid tissue, which is indistinguishable from parathyroid. This condition of affairs in the avian thyroid has been emphasized by Forsyth, and it has been pointed out that from the very wide variations in the amount of the intervesicular tissue found in different specimens of the same species, and from feeding experiments, we must conclude that the proportion between vesicular and intervesicular tissue varies under different physiological conditions.

The *parathyroid* of birds (see Fig. 57) contains an abundance

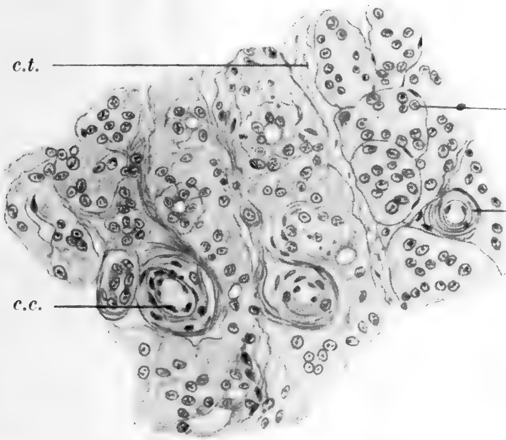


FIG. 57.—Pigeon. Portions of post-branchial body (on the left) and parathyroid (on the right), separated by a connective-tissue septum. Note the presence in both of structures identical with Hassall's corpuscles of the thymus. These are numerous in the post-branchial body, and few in the parathyroid. In both, the concentric bodies frequently show a lumen. (F. D. Thompson.)

c.c., concentric corpuscles ; *c.t.*, connective tissue ; *p. thyr.*, parathyroid.

of fat. It does not contain vesicles like those of the reptilian glandule.

In close relationship, and in some regions anatomically continuous, with the tissue of the parathyroid, we find a body having an extraordinary structure. It is obviously of epithelial nature, and is composed largely of structures which at first sight resemble small arteries, but whose walls are composed entirely of concentrically disposed spindle-shaped cells, and projecting into the lumen are irregular cells lining the tubules (Fig. 57). The rest of the body appears to be made

up of structures identical with the various well-known forms of Hassall's concentric corpuscles of the thymus. There is a mass of this tissue in the centre of the parathyroid, and small portions of it in other regions of the glandule. There are also true thymus nodules in close connection with the body. Thus the structure which is commonly called the *post-branchial* body in birds (a yellowish-white body some little distance posterior to the thyroid), is composed not only of post-branchial tissue, but also of parathyroid and thymus. Although a parathyroid is derived from both third and fourth clefts, yet the one derived from the latter does not become enclosed in the thyroid tissue as is the case in mammals.

8. **Mammalia.**—(*a*) The general position and anatomical relations of the thyroid in mammals is too well known to call for a description. It will, however, be useful to describe in a series of mammals the probable number and the usual position of the parathyroids in relation to the thyroid.

The parathyroids of mammals are usually four in number. They are small, oval, or spherical bodies, in most cases of a distinctly lighter tint than the thyroid tissue, and occupy very variable positions not only in different species, but in different individuals. On either side of the median line of the body there are typically two of these glandules, which are referred to at the present time either as "external" and "internal" or as "parathyroid III" and "parathyroid IV" respectively, the Roman numeral indicating the number of the gill-cleft from whose epithelium the gland was originally formed. The latter mode of signification is by far the most precise, but the majority of writers prefer to refer to an external and an internal glandule on either side. The terms "external" and "internal" appear, however, to be used by different authors in different senses. Kohn's definition of the terms is given in the following words: "Das eine lag in der Regel der Aussenfläche der Seitenlappen lose an das andere innerhalb derselben. Ersteres wurde '*ausseres*,' letzteres '*inneres*' . . . gennant." By "external" and "internal" here is implied "on the surface of" and "in the interior of" respectively. But Schäfer interprets the terms differently. Thus, "there is one parathyroid ('outer epithelial body') constantly to be met with in mammals on the lateral surface of each lobe of

the thyroid, and another on the mesial surface of each lateral lobe ('inner epithelial body')."

Despite this confusion in terminology, for most animals, at any rate, the terms "external" and "internal" are sufficiently suitable for designating the two parathyroids respectively ("III" and "IV"), because it so happens that the glandule which lies on the surface of the gland lies also in the majority of cases on the lateral aspect of the lobe, and the one which is buried in the thyroid substance is nearer the mesial surface.

(*b*) In *Man* the anatomy of the thyroid is too well known to need any description. It belongs to the group of

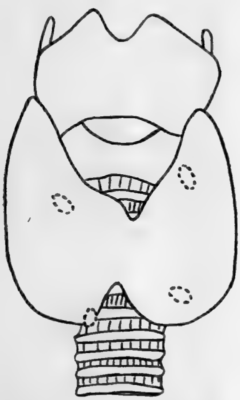


Fig. 58.—Semi-diagrammatic sketch showing the position of the parathyroids, the thyroid, and the trachea in the human subject. Front view. Parathyroids projected on to the surface.

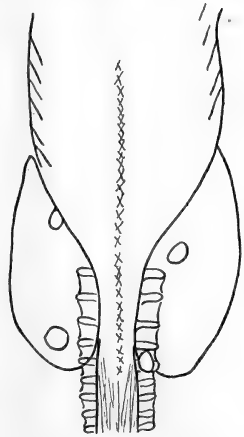


Fig. 59.—Semi-diagrammatic sketch showing the position of the parathyroids in the human subject. Posterior view.

thyroids possessing an isthmus. There are many points of interest, embryological and surgical, connected with some common varieties, but there will not be space to treat of these.

The *parathyroids*, according to most observers, are four in number—two on each side of the median line of the body. The average dimensions are about 6 or 7 millimetres in length, 3 or 4 millimetres in breadth, and 1·5 or 2 millimetres in thickness. The length is very variable, while the thickness is fairly constant. In shape they are oval or pyriform, and

they may be connected by a stalk, in which run the parathyroid vessels, to the thyroid gland. The average weight is 0·035 gramme. There seems to be no relation between the weight of the parathyroids and that of the thyroids. The parathyroids are of a lighter colour than the thyroids, and yellowish owing to the presence of fat. The surface is smooth and soft.

The two glands on each side are described under the names of the "posterior superior parathyroid," and an "anterior inferior" parathyroid, the names indicating their relation to each other. (See Figs. 58 and 59.) The posterior superior glandule is more constant in position than the anterior inferior. It lies usually on the posterior wall of the œsophagus or pharynx at the level of the lower edge of the cricoid cartilage, immediately internal to the posterior margin of the lateral thyroid lobe, and in front of the prevertebral division of the cervical fascia. The parathyroid is usually separated from the thyroid by a septum of connective tissue.

The anterior inferior thyroids are very inconstant in position and relations. Sometimes their position is more anterior, sometimes more posterior, and they may, especially in the former case, be placed very low down, even at the level of the tenth tracheal ring.

(*c*) *Monkey*.—The writer is not acquainted with any description of the parathyroids in the anthropoid apes. In the different species of monkey usually employed for operations in the laboratory, the arrangement of the parathyroids is quite different from that in the human subject. The present writer, working in conjunction with Professor W. A. Jolly, found that in the monkey the thyroid lobes are sometimes united by an isthmus, sometimes unconnected. There is a well-developed isthmus in *Macacus rhesus*, and the parathyroids are four in number, two on each side, and are always, so far as we have seen, embedded in the substance of the thyroid.

(*d*) *Dog*.—The thyroid of the dog usually consists of two distinct lobes unconnected by any isthmus. Ellenberger and Baum, however, state that the thyroid consists of two lateral lobes and an isthmus, which latter structure is wanting in small dogs and present in large ones, while in dogs of medium size it is sometimes present. The lateral lobes are elongated, oval, and taper slightly at oral and aboral ends. They are

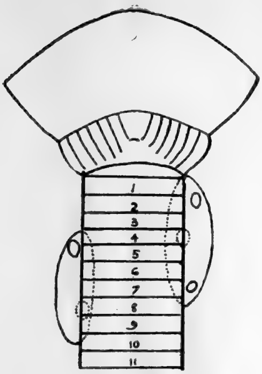


FIG. 60.

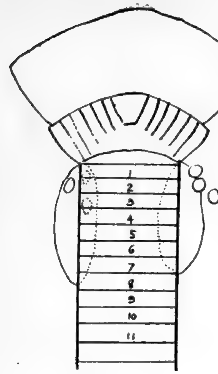


FIG. 61.

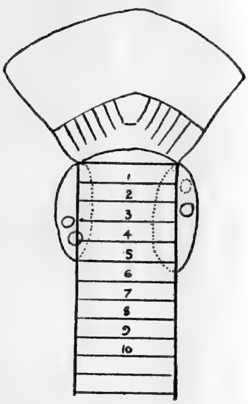


FIG. 62.

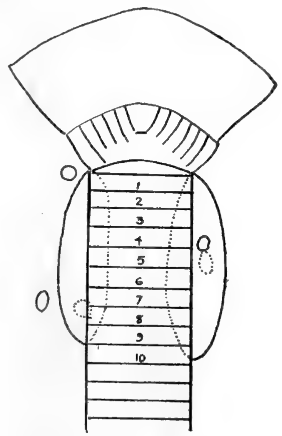


FIG. 63.

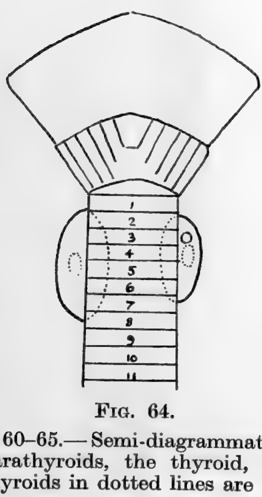


FIG. 64.

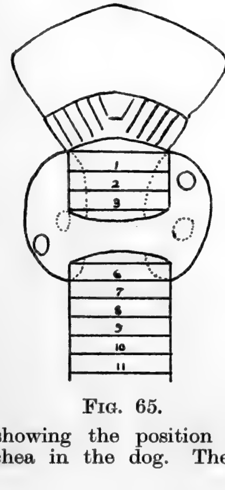


FIG. 65.

FIGS. 60–65.—Semi-diagrammatic sketches showing the position of the parathyroids, the thyroid, and the trachea in the dog. The parathyroids in dotted lines are "internal."

placed at the side of and towards the dorsal aspect of the trachea, immediately aboral from the larynx.

The parathyroids are usually four in number, but there may be as many as five, and sometimes it is not possible to see more than three with the unaided eye. The external parathyroids are as a rule very easily found. Sometimes they are at some distance from the thyroid lobe, while at other times they are more or less embedded in its substance, though never so deeply as the internal glandule. Sometimes their blood supply is such as to permit of their being left behind in the operation of thyroidectomy. This, however, is rare. The internal parathyroid, on the contrary, is small, deep in the thyroid substance, and very variable in position, so that in the living animal the experimenter has frequently to abandon the attempt to find it, while even post mortem it cannot always be revealed except by serial sections. It is very rarely found that the internal parathyroids can be seen on both sides (see Figs. 60–65).

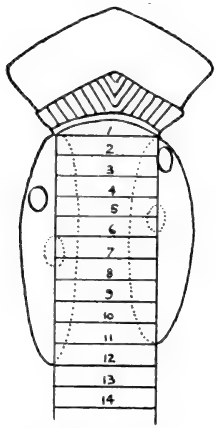


Fig. 66.—Shows the relative positions of the parathyroids, thyroid, and trachea in the cat. This may be described as an average condition of affairs. The "internal" parathyroids are in dotted outline.

(*e*) *Cat.*—In the cat, as is most usual throughout mammals, there are four parathyroids, two internal and two external. Their arrangement resembles that in the dog. (Fig. 66.)

(*f*) *Rabbit.*—There are usually four parathyroids, but the external glandules are uniformly placed at a considerable distance from the thyroid lobe. For this reason, in the earlier extirpation experiments they were always left behind at the time of the operation. (See Figs. 67–71.)

(*g*) In the *Guinea-pig* the distinction between internal and external parathyroids seems largely to break down. There are usually four parathyroids, sometimes three, or even only two. (Figs. 72–76.)

(*h*) In the *Rat* the thyroid consists of two lobes united by an isthmus. There is only one parathyroid in connection with each thyroid lobe, and this seems to correspond with

the external body of the cat and dog. McCarrison states that there is sometimes an internal parathyroid in the rat.

(*i*) In the *Wolf* and *Badger* there are four parathyroids whose precise location does not call for any description.

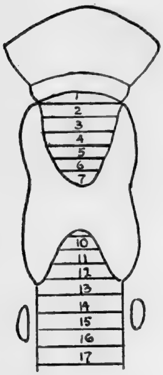


FIG. 67.

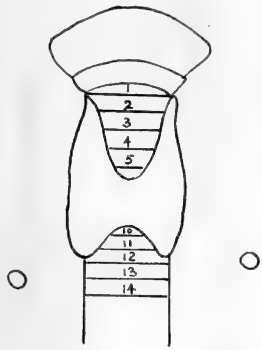


FIG. 68.

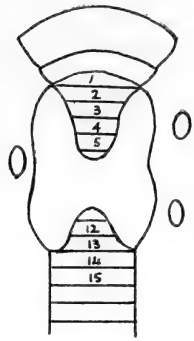


FIG. 69.

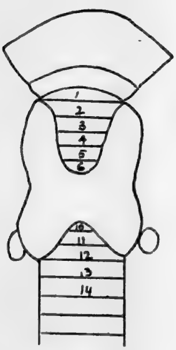


FIG. 70.

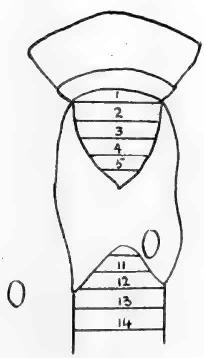


FIG. 71.

FIGS. 67 to 71 are semi-diagrammatic, and show the relationship of the thyroid, external parathyroids, and trachea in a series of rabbits. The "internal" parathyroid is not shown, since it was found only on microscopical examination.

The general arrangement conforms fairly closely with that in the dog and cat.

(*j*) In the *Pig* the internal parathyroid is stated to be absent. In this animal and in *Ruminants* the external parathyroid is not close to the thyroid, but is in connection with

the thymus. In the ox, in addition to the four typical parathyroids, it is stated that there are accessory parathyroids of macroscopic size in different regions of the neck and mediastinum.

(*k*) In the *Horse* the relationships of the parathyroids have

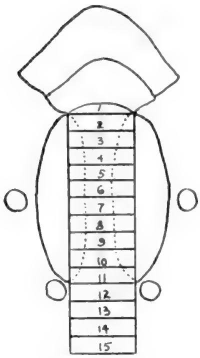


FIG. 72.

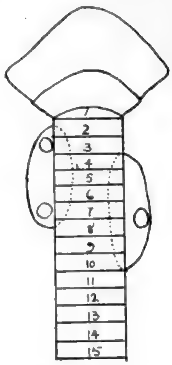


FIG. 73.

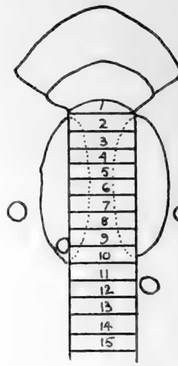


FIG. 74.

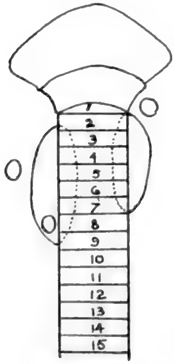


FIG. 75.

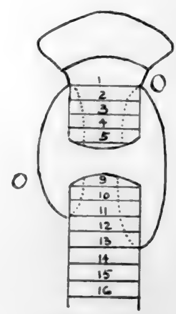


FIG. 76.

FIGS. 72 to 76.—Parathyroids in the guinea-pig. The extreme variability in number and position is shown. In none of this series were any true "internal" parathyroids seen with the unaided eye.

not been fully ascertained. In a recent paper Estes states that the external glandule of the horse is found in close relation to the upper end of the thyroid or in the perithyroid areolar tissue. The internal parathyroid is variously placed beneath the capsule of the thyroid, usually near its upper pole. The external gland is much the larger. The horse then appears

to resemble the other Herbivora in the distribution of its parathyroids.

(*l*) In *Sheep* and *Goats* there are two parathyroids embedded more or less in the thymus, and two others in the substance of the thyroid. The thyroid of the sheep varies extremely in size in different individuals.

C. Histology of the Thyroid in Man and Mammals

The larger lobes of the thyroid are surrounded by a thin capsule of connective tissue, and are divided, by processes

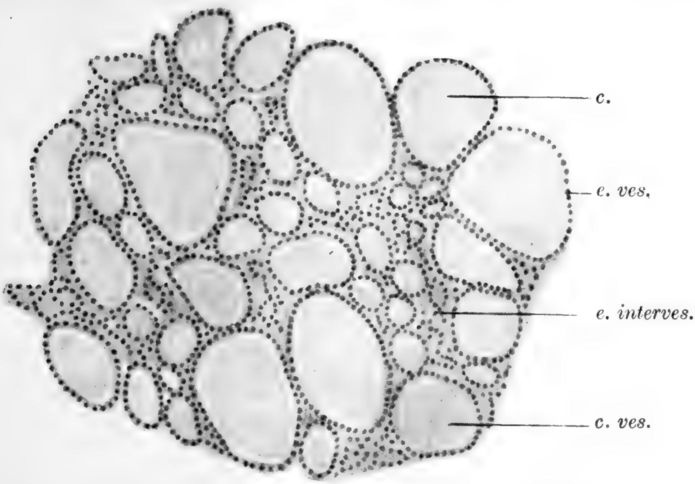


FIG. 77.—Thyroid of normal dog. (× 120.)
c., colloid ; *e. ves.*, epithelium lining vesicles ; *e. interves.*, ephitelial intervesicular tissue ; *c. ves.*, colloid vesicles.

running into the interior of the organ, into smaller and smaller lobules. The ultimate lobules are of irregular form and size, but are, for the most part, roughly circular or oval in section, and have a diameter of about 0·5 to 1·0 millimetres. The interior is mostly occupied by vesicles of varying size, 45 μ to 110 μ, and varying shape. It was formerly thought that the gland was made up of a system of branching alveolated canals, but it has been conclusively shown that the glandular substance is composed of closed vesicles, which are separated from one another by fine strands of connective tissue, and a variable amount of an intervesicular cellular tissue. Most of these

vesicles are of roundish, long, oval, or polyhedral form, but occasionally one meets with forms somewhat resembling the tubules of alveolar glands, only that they are closed at both ends; these have sometimes side branches, or two or three large vesicles may freely communicate with each other. In many lobules one finds in addition to the vesicles solid cords and nests of epithelium cells. These are more numerous in the young and developing thyroid.

The ensheathing capsule of the organ and the interlobular connective tissue consist of bundles of white fibres with numerous elastic fibres. This connective tissue carries numerous bloodvessels and lymph vessels into the interior of the lobules, and finally surrounds the vesicles of the gland substance. The vascular connective tissue comes into immediate contact with the epithelial lining of the vesicles. It is said that there is no *membrana propria*; the vesicle is enclosed by very fine bundles of connective-tissue fibres, outside of which is the endothelium of the lymph spaces.

The epithelium cells lining the vesicles are of a fairly uniform, cubical, or columnar form, 9 μ to 13 μ in height. They tend to become flatter in old age, but cylindrical cells are not uncommonly found, even in the adult. When examined in 0·75 per cent. normal saline, the epithelial cells of the human thyroid show, in most instances, a number of granules of varying size. These are chiefly aggregated in the part of the cell next to the cavity of the vesicle; they are highly refractive, and show a characteristic greenish tinge. These are apparently of a fatty nature; but, in addition to these, there are found in the cells smaller granules of a different character. The larger granules appear to be characteristic of human thyroid.

According to Langendorff, the epithelium cells are of two kinds—"Hauptzellen" and "Colloidzellen." In osmic-acid preparations stained with the Ehrlich-Biondi mixture, the former are unstained, while the latter appear red with green nuclei. According to v. Ebner, these do not represent two distinct varieties of element, and there is nothing in the vesicular epithelium corresponding to the two kinds of cell in the glands of the stomach. The cell protoplasm shows a retiform structure, with frequent longitudinal striation. The nuclei are spherical, have a homogeneous appearance, or show a very fine chromatin network. As in other gland epithelia, mitosis is

only to be observed in young individuals. Zimmerman describes a double centrosome close to the free surface of the cell.

Occasionally one finds solitary cells in the interior of a vesicle. These are normal epithelium cells, which have become separated from the lining layer of the vesicle. Sometimes they are in a good state of preservation; mostly, however, they appear to be in some stage of resorption. The nucleus stains faintly. According to v. Ebner, leucocytes do not occur either in the epithelium or in the cavity of the normal vesicle.

As regards the contents of the vesicles, they are filled with the yellowish sticky fluid which is observed to flow from the surface when the gland is cut. The abundant presence of cells and their debris in the interior of the vesicle may be due to post-mortem changes. Verson states that the free surface of the cell wall may be seen to project irregularly, and spheroidal, tenacious, and hyaline drops, which after some time coalesce in the centre of the vesicle, gradually develop from the bodies of the cells.

Peremeschko found that the contents of the vesicles change with the age of the animal. In young embryos there is a finely granular mass, enclosing cells and nuclei. In larger embryos one finds occasionally vesicles filled with transparent masses of colloid; in young animals this is the case with the larger number of the vesicles, and in adults one rarely finds vesicles without colloid. In adult animals the colloid substance completely fills the cavity of the vesicles.

Zeiss looks upon the colloid as nothing more than a concentrated form of the fluid originally appearing in the vesicles. In this fluid he often finds a lump of colloidal material, around the periphery of which new layers of colloid are being continually laid down, until the entire cavity is filled with a compact mass of colloid. The drops of secretion described by Peremeschko, Zeiss considers to be simply appearances due to shrinkage. He was never able to isolate the clear, transparent, unstainable drops.

Baber finds in the vesicles, in addition to a small quantity of a clear substance, a solid mass which has retracted from the wall of the vesicle. By staining with picrocarmine it shows a finely granular structure, and is strongly differentiated by its yellow colour from the red-stained epithelial wall. Hæmatoxy-

lin gives it an opaque grey or greyish-violet tinge, and shows a homogeneous or granular structure. The vesicle varies from time to time both as to the amount of the contents and as to their staining reactions, depending upon the state of functional activity of the gland.

According to Biondi, the vesicles contain a homogeneous substance which becomes dark and granular after fixation with osmic acid. This substance is a product of the epithelial cells, as shown by the fact that these frequently contain granules which have the same staining reaction as the colloid.

Langendorff was the first to give a clear account of the micro-chemical reactions of the colloid substance. There is no doubt that the contents of the gland vesicles completely fill their interior. If these contents become hard as the result of chemical treatment, they may either preserve their original volume or may undergo change in this respect ; if the hardening is the result of dehydration or heat, considerable shrinkage occurs. The best fixing agents are those which coagulate proteins without change of form, such as osmic-acid mixtures. If such be employed, one sees that the masses of colloid lie in close contact with the follicular epithelium, and have a perfectly homogeneous aspect. Langendorff's micro-chemical tests were carried out upon the gland of the calf and the rabbit, which were hardened in alcohol. Acetic acid caused enormous swelling of the vesicular contents, which were rendered transparent. By washing with 0·6 per cent. NaCl one could restore their former appearance. A 0·2 per cent. solution of HCl also caused this swelling ; 33 per cent. KOH or stronger NaOH has the same effect, only to a much less extent. If, now, water be added, rapid breaking up occurs, and only the connective-tissue framework of the glands remains. A 10 per cent. solution of KOH makes the colloid masses indistinct and deliquescent. Strong HNO_3 causes the masses to shrink somewhat ; after some minutes a yellow coloration occurs, even in the cold. This reaction (xanthoproteic) comes on almost instantaneously on heating. Addition of ammonia changes the light yellow tinge into an orange. With pepsin, in presence of 0·2 per cent. HCl, the colloid masses are soon dissolved. Copper sulphate and KOH at 40° C. give a strong violet tinge to the colloid (Biuret reaction). After many hours in the reagent the colloid masses also give Millon's test. If a section

be treated with acetic acid until considerable swelling occurs, and then, after washing, be treated with sulphuric acid, a violet coloration is perceived (Adamkiewicz's reaction).

The colloid masses are not dissolved in boiling water, but are coagulated. The colloid is also coagulated by the other ordinarily used fixing and hardening reagents. These are alcohol, inorganic acids, solutions of metallic salts, and picric acid.

Langendorff considers that the colloid masses are composed either of protein or a substance containing a large proportion of protein. Mucin is not present, as the reaction to acetic acid shows. The protein can hardly be alkali-albuminate, since it coagulates on heating. It may possibly be an alkali albumin modified by containing abundance of sodium chloride. The reactions do not allow of the supposition that any appreciable amount of globulin is present.

The staining power of the colloid is considerable. With picrocarmine the colloid appears bright yellow. If one stains with ammoniacal carmine the colloid takes on the carmine tint very slightly. Eosin and the rest of the aniline dyes stain the colloid powerfully. After treatment with osmic acid or mixtures containing it, the colloid masses are stained dark; the reduction is particularly marked if one stains for a short time with Ehrlich's hæmatoxylin. After long treatment with logwood the colloid becomes bluish-grey or violet.

The consensus of opinion at the present time is that the colloid material arises as a secretion from the epithelial cells lining the vesicle. The epithelium consists of cells having all the characters of true glandular cells, and as in these, the secretion is formed as specific granules in the reticular protoplasm.

In the fœtus the structure of the thyroid resembles that of the adult, while in the new-born it is stated to be quite different. It is said that after birth and for some weeks or months, the vesicles shrivel up and the colloid disappears, and the gland consists of elongated or rounded heaps of epithelial cells, closely pressed together. It is possible that this change after birth is pathological.

D. The Intervesicular Cellular Tissue of the Thyroid

It has been stated above that "in many lobules one finds in addition to the vesicles solid cords and nests of epithelium cells, and that these are more numerous in the young and developing thyroid." It will be desirable to call particular attention to this intervesicular material. This tissue very closely resembles that forming the parathyroids.

The amount of the intervesicular cellular material varies within very wide limits in the thyroid of different species of animals, in different individuals of the same species, and, to some extent also, in different regions of the same gland. It is not rare to find a pair of vesicles in close juxtaposition to each other, so that the colloid of one is separated from the colloid of the other by nothing more than two rows of vesicular cells. In other cases there is a certain amount of connective tissue separating the vesicles; but, speaking for mammals generally, it is more usual to find, separating the colloid vesicles from one another, a variable mass composed of cells which are almost identical in size, nature of cytoplasm, size and form of nucleus, with those lining the colloid vesicles. This intervesicular cellular tissue is proportionately much greater where the vesicles are small. This is notably the case in the rabbit, and is also strikingly true in young animals generally (see above, p. 271). In the monkey the amount of intervesicular tissue is proportionately great, and it is not possible to determine any fundamental differences between its cells and those of the vesicles. In the human thyroid there is often as much intervesicular as vesicular material.

This intervesicular cellular substance is shown in Fig. 77.

E. Structure of the Parathyroids

The parathyroids in man are built up of closely packed polygonal cells, which are divided up by connective-tissue septa into masses and cords of varying sizes and shapes. The glandules are usually surrounded by their own capsule; but in the case of those placed on the surface of the thyroid, the connective-tissue sheath is seen to be derived from, and continuous with, that of the thyroid lobe. The capsule

sends septa into the interior of the organ, which septa convey bloodvessels and nerves destined for the supply of the gland substance.

The protoplasm of the cells often appears to be homogeneous; it does not stain well with eosin, and is vacuolated. The nuclei are spherical and about 4 μ in diameter, and frequently show a chromatic network. Permeating the whole glandule, and even separating the individual cells in many places, is a delicate network of fine fibres, which appear to be of a distinct nature from ordinary connective tissue. It is stained by eosin and faintly also by orcein. Near the periphery of the organ the cells are smaller and lack this special sheath.

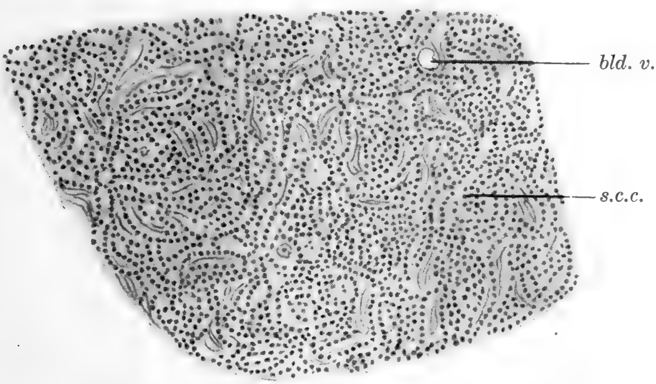


FIG. 78.—Normal parathyroid of dog. (× 120).
s.c.c., solid columns of cells; *bld. v.*, bloodvessel.

In man and different mammals, Kohn distinguishes three different arrangements of the epithelium cells which may be met with: (1) A compact cell mass; (2) a retiform tissue; and (3) a lobular conformation. These different arrangements are not characteristic of any species or any age, but may be found side by side in the same glandule.

In the cat the internal parathyroid has a peripheral layer of cylindrical cells, and there appear to be other differences in structure between this body and the external parathyroid. Thus the cells are not so closely packed in the internal as in the external gland, and their outlines are more easily distinguished. Further, the cell nuclei of the internal parathyroid do not stain so deeply as those of the external body. This

last difference, however, can only be detected in adult animals. In some species, as the rabbit, the internal parathyroid is intimately connected with a "central canal" (post-branchial body) and with the thyroid itself.

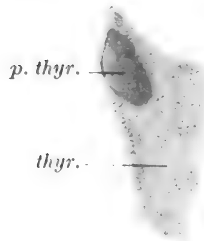


Fig. 79.—Human. A drawing, as seen under a simple lens of a portion of the thyroid and a parathyroid which is considerably hypertrophied and otherwise modified. The specimen is pathological, but there is no record of the patient. The object of this figure is to show that the structure in question is in reality morphologically and topographically a parathyroid.

p. thyr., parathyroid; *thyr.*, thryoid.

In close contact with each of the parathyroids we may find a thymus nodule, and occasionally the central portion of this last is seen to be directly continuous with the tissue

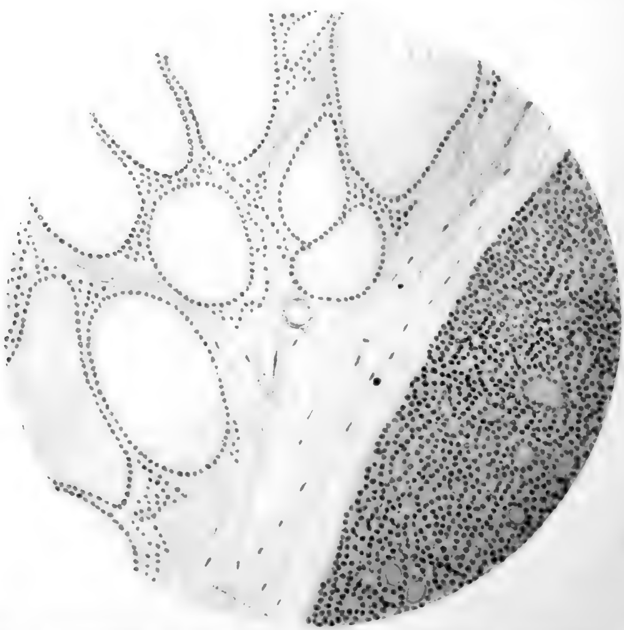


Fig. 80.—A portion of the thyroid and neighbouring parathyroid, with a fairly thick connective-tissue partition; low power. On the left we see the colloid vesicles of the thyroid; on the right the parathyroid, which is of a typical parathyroid structure near the connective-tissue septum; but which shows several undoubted colloid vesicles in the left-hand portion of the drawing.

of the parathyroid. Again, parathyroids may be found either in the cortex or in the medulla of the thymus gland. When we bear in mind the development of these various organs (see below, pp. 277 and 279), such intimate anatomical connections and occasionally even apparent confusions are not astonishing.

In some cases the parathyroids are found to contain colloid vesicles. Figs. 80 and 81 illustrate this very clearly. The drawings represent what topographically is, or, to be more correct, *was*, parathyroid; but many parts of the substance are studded with colloid vesicles.

F. Development of the Thyroid

The thyroid is the chief of the organs arising from, or in close topographical relation to, the gill-clefts. Other organs in the same group are the thymus, the parathyroids, the post-branchial bodies, and the branchial bodies of the Anura.

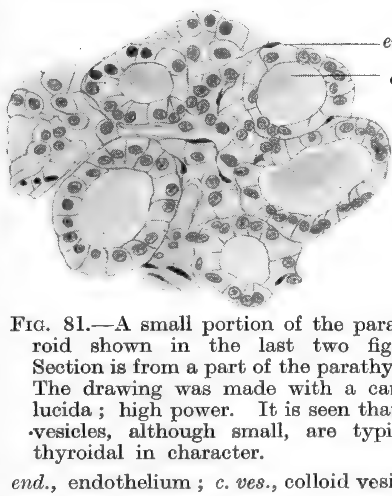


Fig. 81.—A small portion of the parathyroid shown in the last two figures. Section is from a part of the parathyroid. The drawing was made with a camera lucida; high power. It is seen that the vesicles, although small, are typically thyroidal in character.

end., endothelium; *c. ves.*, colloid vesicle.

The origin of the thyroid is practically the same throughout vertebrates. It arises from the ventral wall of the pharynx in its anterior region, as an unpaired outward projection of epithelium. As stated above, in Amphioxus and Ammocœtes, the opening into the buccal alimentary tube remains patent, and the thyroid appears to be an organ of very ancient origin, which shows relationship to the hypobranchial furrow of Tunicates. In Petromyzon the organ detaches itself completely from its place of origin, the opening becomes closed, and a number of closed vesicles are formed, lined with cylindrical epithelium, and containing colloid.

In all vertebrates above the Cyclostomata the unpaired rudiment of the thyroid arises as an evagination of the floor

of the pharynx between the bases of the first and second branchial arches. The structure then separates itself completely from its original point of growth, and appears as a closed vesicle. In fishes the organ remains unpaired, but in Amphibia it divides into two portions whose position differs in different species.

In the Sauropsida the origin of the thyroid is very similar. The original vesicle becomes a compact organ, and in Lacerta becomes developed into a bilobed organ with a median isthmus. In the interior one can for a long time trace a lumen which is the remains of the aperture of the original vesicle. This is lined with cylindrical epithelium. The colloid-containing vesicles do not, however, communicate with a canal.

In birds the two lobes become quite separate.

The origin of the thyroid in mammals has been, and still is, a matter of considerable controversy. There can be no doubt about the median rudiment, which arises in the same way as in other vertebrates—*i.e.*, as an evagination of the floor of the pharynx between the first and second branchial arches. In the human embryo the evagination is a small pouch beginning to expand laterally in an embryo of 5 millimetres in length ; in an embryo of 10 millimetres the lateral expansion has much increased, and there is a median duct, the opening of which upon the surface of the tongue corresponds to the *foramen cæcum* ; the duct itself is known as the *ductus thyreo-glossus.* The whole structure now consists of a bilateral epithelial vesicle connected by a slender hollow pedicle with the surface of the tongue. The duct persists up to the eighth week, gradually elongating as the thyroid and the tongue separate. The duct usually begins to be obliterated during the fifth week, but sometimes persists. After the fifth week the vesicular portion expands rapidly.

The development in other mammals does not call for a separate description.

Many authors describe a lateral rudiment in addition to the median, and this is accepted as the true account by the authors of some textbooks, but this lateral rudiment appears to be that of the post-branchial body (*vide infra*, p. 279).

In most mammals the thyroid remains a single organ, consisting, as in man, of two lobes, with a connecting isthmus.

In some, however, the right and left lobes are completely separate. The colloid does not begin to be formed in mammals till towards the end of fœtal life, and sometimes even not till after birth.

But before going further it will be necessary to give some account of the *post-branchial bodies*, which are present in all Gnathostomata except Heptanchus and Teleosts.

In Selachii the organ was first observed by v. Bemmelen, who called it the "suprapericardial body." He describes it as an evagination of the ventral wall of the pharynx *behind the last gill-cleft.* This becomes separate from the wall of the pharynx, and now consists of a vesicle lined with epithelium cells. It bears some resemblance to the original rudiment of the median thyroid, and soon consists of a mass of separate vesicles. Whether these contain colloid is not known.

In Amphibia, Reptilia, and Aves, the post-branchial body is formed as an evagination behind the last gill-cleft, sometimes, however, only unilaterally. In these classes of animal the vesicles never contain colloid.

Of peculiar interest are the researches of Maurer upon Echidna. In this animal, as in all vertebrates, the post-branchial body arises behind the fourth gill-cleft, and soon develops into a gland having a structure like that of the thyroid, the important point being that *colloid is contained in the vesicles.* In Echidna these post-branchial bodies (colloid glands) never unite with the thyroid proper, which is a large gland, with two lobes and a connecting isthmus.

In other mammals the post-branchial bodies may assume a structure identical with that of the median thyroid. How much, if any, of the fully developed thyroid is derived from the post-branchial bodies still remains an open question.

G. Development of the Parathyroids and some other Branchial Cleft Organs

The development of the thymus will be treated hereafter (p. 225), but it will be convenient in this place to deal with the development of the parathyroids and the thymus nodules found in connection with the thyroid.

The particular gill-clefts with which we are at present specially concerned are the third and fourth.

From the epithelium on the ventral aspect of the third cleft arises the main portion of the thymus. This may be called "thymus III." (see Fig. 82, p. 281). The ventral proliferation of the epithelium of the fourth cleft also gives rise to thymus tissue, but this is usually simply a small nodule in the substance of the thyroid, and is called "thymus IV."

The dorsal aspects of the third and fourth clefts show thickenings of the epithelium which, however, do not develop into thymus tissue, but retain a typical "epithelial" structure. These are the parathyroids named respectively "parathyroid III." and "parathyroid IV." In connection with the last is found a cavity lined with epithelium. This is the post-branchial body.

The thymus nodule sometimes found in close relation to the external parathyroid ("parathyroid III.") is simply an isolated portion of the main thymus ("thymus III.").

The accompanying diagrams (from Kohn) will help to make the matter clear (Figs. 82, A and B).

Explanation of Fig. 82.

(*Diagrams A and* B.)

A. illustrates the development of the branchial organs of mammals, B. shows their actual relations in the adult.

The different related rudiments of the same branchiomere are represented by a similar direction of shading lines; so also the corresponding organs. Thus the rudiments from the third cleft are represented in A. by horizontal lines, as also the organs thus arising in B. The rudiments and organs from the fourth cleft are characterized by vertical lines. The post-branchial body is shown in thick outline, the thyroid by crossed lines.

The different kinds of tissue arising from one and the same branchiomere are indicated by differences in the shading. The parathyroid tissue is shown by lines, the thymus tissue by alternate continuous and interrupted lines. The post-branchial body is represented in the developed condition as a hollow space with several glandular nodules (shown in dark circles).

A. shows the four internal gill slits (I. to IV.), the epithelial origins of the parathyroids (*p. thyr.* III., *p. thyr.* IV.), the origin of the thymus (*thym.* III., *thym.* IV.), the rudiment of the thyroid (*thyr.*), and that of the post-branchial body (*p.b.b.*).

B. represents a schematic transverse section through the fully developed thyroid (at about the level of the junction of the upper and middle third of the thyroid lobe of a cat). The lettering corresponds to that in Diagram A. The structures which arise from the third cleft become the "external" parathyroid and thymus nodule (separated fragment of thymus III.); those which arise from the fourth cleft become the "internal" parathyroid and the thymus nodule (*p. thyr.* IV., and *thym.* IV.). The post-branchial body is surrounded by thyroid tissue.

(A. is after Groschuff in ruminants; B. from Kohn in the cat.)

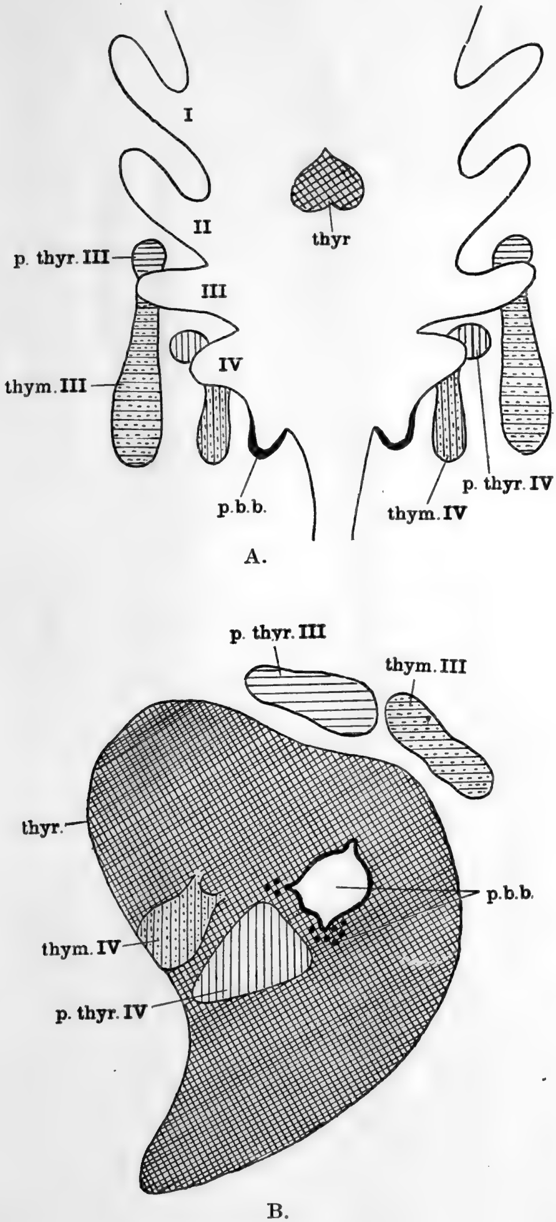

I
II
thyr
p. thyr. III
III
IV
thym. III
p.b.b.
p. thyr. IV
thym. IV
A.
p. thyr. III
thym. III
thyr.
p.b.b.
thym. IV
p. thyr. IV
B.

Fig. 82.

H. Diseases of the Thyroid

Thyroiditis acuta, carcinoma, sarcoma, syphilis, tuberculosis, and echinococcus are all known, but apparently none of these lesions give rise to any of those symptoms usually associated with absence of thyroid function—viz., myxœdema, cretinism, etc. This seems to be the case even when gangrene occurs.

The diseases which will be referred to are—(1) Goitre, (2) endemic cretinism, (3) myxœdema, (4) cachexia strumipriva, and (5) Graves's disease.

1. *Goitre*

The ætiology of endemic goitre is a long-standing puzzle, and there are many aspects of the question which still remain in obscurity. The distribution of the disease is so extraordinary and so well known that it need not be described here. It is now generally recognized that it is an infection due to a living germ confined to certain geological formations, and transmitted to man by means of drinking-water.

McCarrison, from observations carried out in Gilgit, Kashmir, concludes that goitre can be experimentally produced in man by the administration of the matter in suspension separated by filtration from waters that are known to be goitre-producing. Goitre cannot be produced when the suspended matter is boiled. The disease is due, therefore, not to mineral, but to the living component of the suspended matter—in other words, to a living organism of disease. The incubation period of experimentally produced goitre is usually about ten to fifteen days. Goitre can be cured by the administration of intestinal antiseptics. Thus the lactic-acid ferments exercise a curative action when applied to the treatment of incipient goitres. It is probable, therefore, that the organism which is the cause of the disease is parasitic in the human intestine. The fæces of most cases of goitre in Gilgit show a plentiful amœbic infection, but whether the disease is due to this infection has not been determined. The disease cannot be communicated to dogs by means of extracts from the fæces of goitrous individuals. Bircher finds that filtering does not destroy the contagion, while boiling does. This theory of McCarrison has not been universally accepted.

Professor Cameron and myself have recently described an enlarged thyroid in an Elasmobranch fish—*Squalus Mecklii.* The structure showed active hyperplasia and in certain parts all the appearances of true carcinoma. We are not aware of any previous observations on thyroid growths in Elasmobranchs. Teleostean thyroid enlargements have been described by Marine and others. One of the chief points of interest about the Teleostean growths is that the gland is unencapsuled and consists of scattered vesicles and groups of vesicles. The Elasmobranch thyroid, on the other hand, is definitely encapsuled, and forms a compact organ. Again the change we have described occurred in a wild fish, and one for which a constant supply of iodine is readily accessible. Marine finds that in fresh-water fishes iodine is a valuable curative agent.

It is usual to classify goitres as parenchymatous, vascular, and cystic. But Marine has emphasized the importance of a physiological cycle as explaining the innumerable forms of goitre.

In interpreting the thyroid changes in goitre, according to Marine, one must bear in mind the simple thyroid cycle which, beginning with the normal cell, consists of progressive changes through all degrees of hypertrophy and hyperplasia and regressive changes either (1) throughout all degrees of atrophy, or (2) throughout all degrees of involution to the resting or colloid or nearest normal state that such thyroids can again assume which have once undergone hyperplasia.

The cycle may be represented schematically as follows :—

$$\text{Normal thyroid—hypertrophy—hyperplasia}\begin{cases}\text{atrophy}\\ \text{involution to colloid state}\end{cases}$$

$$\text{Colloid state—hypertrophy—hyperplasia}\begin{cases}\text{atrophy}\\ \text{involution to colloid state}\end{cases}$$

Colloid . . . .

This conception has made it possible to interpret the many gradations of thyroid reactions found in diffuse overgrowths of the thyroid (goitre), and now one looks upon any given

specimen of thyroid reaction as a phase of this cycle and not as an entity either anatomically or physiologically.

Iodine is usually recommended for goitre, especially in its early stages.

2. *Endemic Cretinism*

The precise relationship between goitre and cretinism has been the subject of much discussion and speculation.

FIG. 83.—Cretin before treatment. Age 28 (June, 1895). Height 34½ in. (From Murray.)

The subject has recently been reinvestigated by McCarrison in the Chitral and Gilgit Valleys. He concludes that the degree to which cretinism is associated with goitre is determined by the age of the endemic, and varies directly with the extent to which the latter disease prevails among the adult population. Cretinism is rarely, if ever, due to the development of a goitre in the individual. The thyroid enlargement is, or may be, an effect; it is not the cause of the disease. Defective thyroid function in the mother is the essential factor in the production of cretinism.

Cretinism is due to the action of toxic agents, notably that of endemic goitre, on the developing thyroid of the unborn child. The thyroid defect is congenital, but it may remain latent pending its manifestation through the impulse of some accidental circumstance.

The symptoms of cretinism have been so often and so fully

described that it is unnecessary to make more than a brief reference to some of them. The changes in the skin are stated by many observers to be identical with those found in myxœdema.

McCarrison states that in the Chitral and Gilgit Valleys there are two distinct types of the disease—(1) the myxœdematous type, and (2) the nervous type. Cases commonly present the clinical features of a combination of these. Deaf-mutism is an almost constant accompaniment of both types of the disease. The myxœdematous type corresponds with the form met with in Europe.

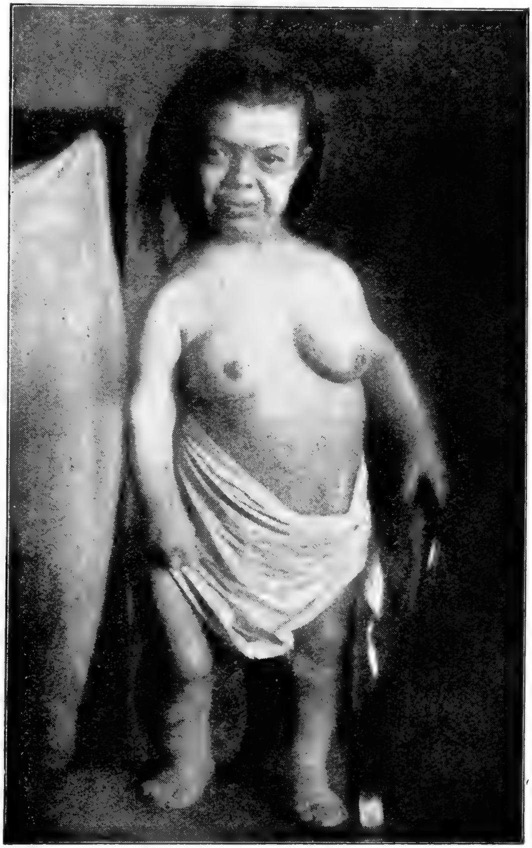


FIG. 84.—Cretin after treatment. February, 1899. Height $38\frac{1}{2}$ in. (From Murray.)

The nervous cretins are helpless, and usually deaf and dumb. There is a "knock-kneed" spasticity of the lower limbs, increased knee-jerk, and there may be marked flexion of the toes on the sole. The upper limbs assume a position of right-angled flexion; the thumb may be drawn into the palm and the fingers closed over it, whilst the wrist is flexed. Among other nervous symptoms are movements of the head, grimaces, convulsions, nystagmus, and internal strabismus, and idiocy. It is impor-

tant to note that these nervous cases are considerably benefited by treatment with sheep's thyroid. Cretinism is often classified as a form of infantilism (*q.v.*, p. 380).

3. *Myxœdema*

(*a*) *Symptomology.*—In 1874 Sir William Gull communicated to the Clinical Society of London a paper bearing the title, "On a Cretinoid State supervening in Adult Life in Women." This account was based upon five cases. In 1877 Ord proposed the name "myxœdema," which has ever since been employed. This writer describes changes in the thyroid. Curling and Fagge had previously described atrophy of the gland in cretinism. The early history of the subject may be completed by referring to the work of Charcot, who called the disease "cachexie pachydermique"; Savill, who first described a case in a male subject; and Hadden, who first definitely ascertained that atrophy of the thyroid is commonly associated with myxœdema.

The ætiology of myxœdema is obscure. Heredity, traumatism, tubercular family history, alcohol, syphilis, and many other factors have been alleged. The disease is chronic, and the onset is very gradual.

In most cases myxœdema shows itself in a gradual swelling of the skin. This may be accompanied by nervous disorders, neuralgia, convulsions, "tetany," mental disturbances, and skin diseases. The swelling of the skin is at first most noticeable on the face. The chin, eyelids, nose, lips, and cheeks swell up, and the palpebral cleft is narrowed. A slowly increasing languor is often felt in early stages, and a sensitiveness to cold is frequently noticed. Headache is an early symptom in some cases.

The skin may become yellowish, and shows in fully developed cases what is called "solid œdema." The swelling resembles œdema or fat, but on palpation feels softer and more elastic than fat, and unlike ordinary œdema, it does not pit on pressure, nor does any fluid exude if the skin is pricked. The weight of the patient is increased very considerably. The skin is wrinkled in some regions, pendulous in others. The swelling is fairly uniform over the trunk and limbs, but is most noticeable in the hands and feet. The skin becomes dry and rough and

FIG. 85.—Myxœdema in man aged 44 of two years' duration before treatment. (From Murray.)

FIG. 86.—Same case after six weeks' treatment by thyroid extract. (From Murray.)

cold. In later stages of the disease perspiration may be entirely absent. Warts and moles may occur.

The hair becomes thin and scanty. In some cases the head is almost completely bald, and the skin of the scalp becomes dry, brown, and scaly. The teeth often become brittle and carious. The mucous membranes may be swollen, and there is dryness in the mouth and nose. In fully developed cases the temperature is almost continuously one, two, or three degrees below normal. Mental dulness, drowsiness, and slowness of reaction are characteristic of most marked cases. There may be hallucinations going on to definite insanity. Sight, hearing, taste, and smell are often more or less impaired, and sexual feeling may be diminished.

We shall see later on (p. 289) how far these symptoms correspond with those observed in human beings after operations upon the thyroid, and in animals after experimental thyroidectomy (p. 300).

(*b*) *Morbid Anatomy.*—The most interesting changes are found in the thyroid lobes. The Myxœdema Committee in 1858 found that out of fifteen cases in which the thyroid was examined post mortem, there were six of atrophy of the glands, and all were diminished in size, of a pale yellowish-white colour, hard, and fibrous. There was a connective-tissue overgrowth which led to a destruction of the parenchyma. At the same time there was a new formation of lymphatic tissue.

Similar conditions have been reported by other observers. The cells of the vesicles are reduced in number, and their nuclei in staining capacity. The intervesicular tissue is œdematous and poor in nuclei and in fibrils.

The pathological process consists of a very slowly progressive atrophy. In most cases this seems not to be the result of ordinary inflammatory processes, though Ponfick records diminution in size of the thyroid as a result of a violent interstitial inflammation. Even when the thyroid is increased in dimensions, as occasionally happens, the vesicular substance has for the most part disappeared, and its place has been taken by interstitial growth.

In the skin the connective tissue of the corium has its elements torn asunder. The fibres are hyperplastic. The cell nuclei and the fibrils of the gelatinous substance between the fat lobules are multiplied. The whole tissue has a trans-

parent appearance. It is as if the skin were saturated with a semi-fluid substance. Peculiar, glistening, highly refractive bodies, whose nature is not known, have been found. A similar condition is reported in other organs and tissues.

The chemical nature of the infiltration is not certainly known. It is very doubtful whether it is mucin, and there are many reasons for thinking that it has not the composition of ordinary œdema. Cases in which a chemical examination of the skin may be carried out are so rare that it will probably be many years before the matter can be satisfactorily settled. Ewald thinks that there is a trophic change in the direction of degeneration of fatty tissue or a persistence of the embryonic mucous tissue.

(c) *Pathogeny.*—In the view of perhaps the majority of physicians and pathologists who have studied the subject, the pathogeny of myxœdema is very simple. Thus, Murray says: "These facts clearly show that myxœdema in man is entirely and solely due to disease or removal of the thyroid gland and the consequent failure of the supply of its internal secretion." We have seen (p. 140) that in the case of Addison's disease it is difficult or impossible to produce artificially the symptoms of this disease by extirpation of the adrenals in animals. The most striking of all the symptoms—namely, pigmentation of the skin—does not occur in the operated animals. Similarly we shall see (p. 303) that in animals deprived of their thyroids swelling of the skin and subcutaneous tissues is, at any rate, not a common symptom, and according to some observers cannot be induced at all. It must be remembered, however, that it is scarcely possible to imitate artificially the exceedingly gradual fibrosis and destruction of glandular tissue which occurs in myxœdema.

The parathyroids are intact according to the majority of observations, but there is some evidence that the pituitary body may be concerned.

4. *Cachexia Strumipriva*

In 1882 Reverdin described the results of goitre extirpation. In the following year Kocher published his classical report on eighteen cases. Later in the same year J. and A. Reverdin noted the resemblance of the symptoms to those described by Gull, and hence called the condition "operative myxœdema."

Kocher's term was "cachexia strumipriva." "Cachexia thyreopriva" is a more correct term, but is less usually employed.

It is important to note carefully the symptoms recorded when the thyroid is totally removed from the human subject. The cachexia comes on at a very variable period after the operation—from six to eight days up to months or years. Patients advanced in years suffer less than young people under twenty. The patients first complain of fatigue, weakness, and heaviness in the limbs, sometimes associated with pains, tremblings, and sensations of cold. There is a diminution of mental activity, loss of memory, slowness of thought, speech, and movements. Then one notices fugitive swellings of the face, hands, and feet, which gradually become stationary and lead to a coarseness and puffiness of the whole body. The skin loses its suppleness, and becomes infiltrated, dry, and scaly. The hairs of the head fall out.

There are also nervous symptoms, such as are observed in myxœdema. The symptoms, in fact, as they were described by Kocher and Reverdin, are very much like those of myxœdema, except, perhaps, that not so much stress is laid on the "solid œdema."

The majority of writers since the year 1896 have assumed that the precise nature of the symptoms depends on the amount of injury inflicted upon the parathyroid bodies—in other words, that myxœdema properly so called is due to the absence of thyroid functions, while the nervous symptoms (tetany) are due to injury to the parathyroids. This matter will be referred to again when extirpation experiments on animals are dealt with.

5. *Graves's Disease* (*Exophthalmic Goitre, Basedow's Disease*)

The three cardinal symptoms of this disease are tachycardia, exophthalmos, and increase in size of the thyroid gland. Some authors consider that certain nervous symptoms are equal in importance with those here mentioned.

In addition to protrusion of the eyeballs the more important eye signs are (1) a widening of the palpebral clefts or Dalrymple's sign; (2) dissociation of the movements of the eyeball and the upper lid (v. Graefe's sign); (3) inability to maintain convergence of the eyes (Moebius' sign).

Tachycardia is the most important cardio-vascular symptom. A rapid pulse with the patient at rest in the absence of some other obvious cause should always arouse suspicion of Graves's Disease. In the later stages of the disease auricular fibrillation may occur.

Of the cutaneous symptoms, profuse sweating, especially of the palms of the hands and soles of the feet, is the most important.

Diarrhœa, nausea, and vomiting also occur. Accelerated respiration and shallow breathing are suggestive symptoms.

Among the nervous symptoms a marked fine tremor, and restlessness are the most noticeable. Goetsch's test consists in an injection subcutaneously of a small quantity of adrenin. The effect on the pulse rate, the tremor, the blood-pressure, and the subjective nervous symptoms, is closely watched. Acceleration of metabolism is an important feature of Graves's Disease. Though the patients eat large quantities of food they continue to grow emaciated. It is now customary to estimate these changes in metabolism by a study of the basal metabolic rate, by which is meant the minimum heat production when at rest. This is estimated by an analysis of the end products of metabolism, more especially the amount of oxygen used, and of Co_2 given off.

In Graves's Disease there may be a rise in basal metabolism of 50 or 60 per cent.

There may be distinct lymphocytosis as a result of implication of the thymus.

With regard to the pathology of Graves's Disease, it has been discussed whether the primary lesion is in the nervous system or in the thyroid gland. There are certainly changes in the thyroid, though it is not yet absolutely certain that these are constant. It has been shown by Halsted and Edmunds that if a portion of the thyroid be removed from an animal, the remainder shows certain peculiar changes, described as compensatory hypertrophy. The vesicles become irregular or stellate in shape, the lining membrane is folded, the epithelium is proliferated, and the micro-chemical reactions of the secretion are altered so that it stains badly. Now, these changes are practically identical with those found in Graves's Disease. According to Marine, an enormous proportion of stray dogs in Cleveland, Ohio, are thus affected, though they do not show

the symptoms of exophthalmic goitre. Dr. Marine has, however, observed that if these dogs be treated with iodides, the alveoli again become rounded and filled with colloid, and according to Kocher, the administration of iodine will prevent the development of the folded condition after the operative extirpation of part of the thyroid. Changes in the thymus and lymph glands seem to be common.

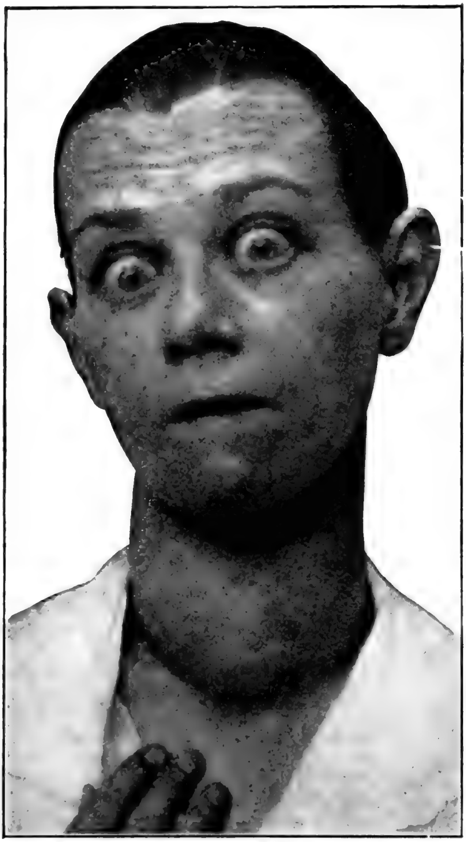


Fig. 87.—Grave's Disease (from Adami).

The most generally accepted theory as to the pathogeny of exophthalmic goitre is that the disease is due to over-activity on the part of the thyroid, that an excess of thyroid secretion is poured into the circulation. But Oswald believes that we have, in fact, a condition of thyroid insufficiency, since the gland is often empty of colloid, and contains relatively little iodine-holding secretion. MacCallum, on the other hand, states that the removal of part of the thyroid improves the condition of the patients, and the administration of thyroid extract makes them worse. The benefit of surgical treatment is urged by several surgeons. Marine and Lenhart do not believe that the thyroid changes in exophthalmic goitre are either primary or specific, or that the thyroids in these cases produce an increased amount of a physiologically active secretion. On the other hand, they think that the thyroid changes

are always secondary to some more fundamental cause, and that there is a hypersecretion quantitatively, but a hyposecretion qualitatively (physiologically); and, lastly, that the usual final stage of all cases, unless terminated by death or relative recovery, is myxœdema.

Reid Hunt has recently found that when small amounts of thyroid are administered to mice for a few days the animals acquire markedly increased resistance to poisoning by acetonitrile. This is believed to be an exceedingly delicate test for thyroid substance. It was found, moreover, that it required nearly twice as much acetonitrile to kill mice which had been fed upon blood from a case of exophthalmic goitre as it did to kill those which had received normal blood. This experiment, Hunt believes, shows that the blood of patients suffering from exophthalmic goitre contains an excessive amount of thyroid secretion.

Apart from surgical proceedings, the treatment consists in absolute rest with the assistance of sedatives if necessary. Serum therapy in the form of Rogers' and Beebe's serum, Rodagen (from the milk of thyroidectomised goats), Antithyroidin and Thyroidectin, may be tried. Local application of iodine preparations may do some good.

If surgical means be employed, we are not yet in a position to state how much of the thyroid gland should be removed in any given case. But in some instances it may be advisable to remove more than one lobe, and it is recommended that a small part of each should be left behind in order to preserve with sufficient certainty the parathyroid glandules.

6. *Other Conditions due to Thyroid Disorder.*

Leopold-Levy and H. de Rothschild believe that in addition to "la grande insuffisance thyroïdienne" there exists a "petite insuffisance thyroïdienne." Under this category they describe a great variety of constitutional and local changes which they ascribe to inadequate action of the thyroid. The symptoms are of the same general character as in myxœdema, only less pronounced. They may, moreover, be complicated by those of hyperthyroidism, or of perverted action of other glands. They describe changes in general appearance, lowering of temperature, loss of appetite, swelling of the salivary glands, delayed development of teeth, dyspepsia, constipation,

diarrhœa, hæmorrhoids, enteritis, affections of the heart and arteries, tendency to catch "colds," affections of the liver, of the urogenital tract and numerous other derangements.

And the final test in all cases as to whether the thyroid gland was really the origin of the trouble is the success of thyroid medication. Since many of the symptoms described are frequently of a temporary or even a trivial character, it is easily to be imagined that they will frequently disappear under thyroid treatment.

Notwithstanding the hypothetical nature of much of this work, yet it may be possible when a large number of critical observations have been made to diagnose and treat minor degrees of thyroid insufficiency.

Slight degrees of hyperthyroidism are probably very common, and may be regarded as almost physiological.

Mongolism is often supposed to be due to thyroid deficiency. The condition is characterized by interference with growth associated with anomalies of the skeleton, falling in of the bridge of the nose, a patent condition of the fontanelles, and defective intellect. At first there is apathy and sleepiness and later dementia. The symptoms are fully developed at birth. It is doubtful whether the primary defect is in the thyroid, though thyroid treatment is sometimes beneficial. The patients are restless and idiotic. The complexion is fair, the eyes are oriental with marked epicanthic folds.

The condition has been supposed to be due to malnutrition of the fœtus *in utero* occurring when a child is born at the end of a long family. Reproductive exhaustion of the mother after prolonged rest from child-bearing has been suggested as a cause. It is said that in these "mongols" the little finger and thumb are always short. The disease was described by Langdon Brown in 1866 as an ethnic degeneration occurring in European children. The condition is fairly common in asylums, where it is often attributed to maternal alcoholism.

Progeria is a name given by Hastings Gilford to a condition in which there is arrest of growth and premature senility. (See p. 380.)

Fœtal and Maternal Athyrosis.—Ennis Smith describes thyroid disturbance prevalent among new-born animals in North America. It affects pigs, sheep, cattle, horses, goats, and dogs. The condition is endemic and appears to correspond to

the distribution of goitre. The most striking feature in typical cases is the absence of hair. The hoofs are thin-walled, short, brittle, and clearly undeveloped. There is hyperplasia of the thyroid, with low iodine content. The pathogenesis is possibly dependent on lack of available iodine, and it is stated that the malady can be overcome by providing abundance of this element in the diet.

I. Diseases of the Parathyroid Glandules

Tetany.[1]—This condition has been known since 1815, but it was not until 1890, after the appearance of Gley's physiological work (*vide infra*, p. 319), that it has been associated with disease of the parathyroids. Many authors have assumed that all forms of tetany are due to hypo-parathyroidism. But it seems more likely that some forms are due to other causes.

Tetany is described as manifest or latent. In the former there are spontaneous attacks of tonic spasm, limited to groups of muscles or involving the whole body. In the latter there is simply an increased excitability of the nervous system, and the tonic spasms may be brought on by external stimuli. The spontaneous spasms involve the muscles supplied by certain nerves and give rise to such characteristic results as the "obstetrical hand." Or there may be laryngospasm and trismus. The increased excitability of the motor nerves is shown by an exaggerated response to the galvanic current (Erb's phenomenon). The large indifferent electrode is placed upon the abdomen and the small electrode is placed upon the point to be stimulated. If a cathodal opening contraction (KOC) occurs with a current below five milliampères in strength, we can be sure that there is increased galvanic excitability of the motor nerves. If cathodal opening contraction does not occur, a small degree of hyperexcitability can be assumed if an anodal opening contraction (AOC) appears with currents feebler than five milliampères.

There is also some hyperexcitability of the sensory nerves.

The "Trousseau phenomenon" is easily elicited in most cases. If the cuff of an ordinary blood-pressure apparatus be applied at the middle of the upper arm and the pressure be

[1] This account is largely taken from Barker.

raised till the arterial flow is interrupted, in cases of tetany the "obstetrical hand" attitude will be assumed.

Much reliance is placed upon "Chvostek's sign" in tetany. The region of the pes anserinus of the facial nerve is tapped and one notes contraction of the muscles of the face. In marked hyperexcitability there may be a contraction of all the muscles of the side of the face stimulated (Chvostek I). When the excitability is somewhat less great, there may be only a movement of the nostrils and a drawing of the angle of the mouth to the side (Chvostek II), while, when there is only slight increase of excitability, there may be only a slight twitch at the angle of the mouth (Chvostek III).

The so-called arm and leg phenomena (Poole) are stated to be useful in diagnosis. In tetany there is a constant response of contracture of the muscles of the upper extremity upon forcible abduction of the arm, and of contracture of the muscles of the lower extremity extended at the knee.

In chronic tetany certain trophic disturbances may occur. Children who have suffered from tetany often show transverse furrows and other defects of the teeth due to faulty development of the enamel. As will be seen below, similar defects are found after parathyroidectomy in animals. In the eye perinuclear cataract has been described.

Many different forms of tetany have been described. Among these may be mentioned the idiopathic tetany of workmen, maternity tetany, gastric tetany, tetany in infection and intoxications, post-operative tetany, and tetany after prolonged forced respiration. It is not to be assumed that all these forms are due to disease of the parathyroids.

Parathyroid treatment does not appear to be of much use, but calcium often does good. Transplantation is almost always impracticable.

It seems reasonable to suppose that a great many different conditions may give rise to the phenomena of "tetany." It has recently been shown that administration of thyroid substance to animals will frequently produce this condition.

Parathyroid insufficiency has also been suspected to be the essential pathological condition in *paralysis agitans*. But hyperfunction has also been alleged to occur in this disease, and the majority of observers fail to find any connection between the parathyroid glandules and the disease in question.

Endemic Tetany.—Endemic tetany, as it occurs in Europe, seems to be a disease of large cities, usually appearing in the spring; it has a tendency to assume epidemic proportions, and it is very local in its distribution.

In India there is an endemic tetany in rural districts. Attention has been specially called to this affection by McCarrison.

The distribution of tetany in India is peculiarly local, and appears to correspond more or less with the distribution of goitre. Sufferers from tetany appear to be able to rid themselves of it by going to a locality where it does not prevail.

In India tetany is a disease of child-bearing women, and there is a marked family tendency to the disease. The children of women who suffer from tetany are frequently cretinous.

Menstruation appears to increase the frequency and the severity of the attacks of tetany, especially so when this function is in any way disordered.

The seasonal prevalence of tetany—its practical limitation to the spring months—is very striking. "Chill," fright, and mental distress often provide the stimulus which produces the spasms. The patients are nearly all goitrous, and incomplete myxœdema may be present.

McCarrison finds thymol very useful in treatment, and this affords proof of the now generally accepted opinion that the spasms of tetany are due to the action of toxic substances absorbed from the alimentary canal. Goitre is an important cause of tetany, because it reduces the efficiency of the thyroid gland.

In various forms of tetany lesions of the parathyroids have been found, but in many cases no such changes are discoverable.

There is no definite syndrome which can be clearly associated with increased function of the parathyroids.

J. Early Views as to the Functions of the Thyroid

According to Handfield-Jones, Galen does not give any very distinct account of the thyroid, but seems to allude to it in his work "On the Use of the Parts of the Human Body." In speaking of the glands of the larynx, he says these "are always found more loose and spongy than others, and which, by the common consent of anatomists, have been created for the

purpose of moistening and bathing all the parts of the larynx and the passage of the throat." Morgagni also quotes the following, which shows that Galen was informed of the absence of a duct: "Now, the neck has two glands in which a moisture is generated. But from the two glands which are in the neck there come forth no vessels by which the moisture may flow out, as those do from the glands of the tongue."

Wharton, in 1656, gives a good account of the anatomy of the thyroid and notes that "it is much more full of blood than any other gland, also more viscid and solid, and more resembling muscular flesh. This is the only difference, that it is not of a fibrous structure but rather of a glutinous nature." He allots four functions to the gland: "(1) The first and principal use of these glands appears to be to take up certain superfluous moistures from the recurrent nerve, and to bring them back again into the vascular system by their own lymph channels. (2) To cherish the cartilages to which they are fixed, which are rather of a chilly nature, by their own heat; for they are copiously supplied with arteries, and abound with blood, from whence they may conveniently impart heat to the neighbouring parts. (3) To conduce by their exhalations to the lubrication of the larynx and so to render the voice smoother, more melodious, and sweeter. (4) To contribute much to the rounded contour and beauty of the neck; for they fill up the empty spaces about the larynx, and make its protuberant parts almost to subside and become smooth, especially in the female sex, to whom on this account a larger gland has been assigned, which renders their necks more even and beautiful."

The third function, it will be noted, is only Galen's view more definitely formulated. This theory, in one form or another, long remained in vogue.

Verheyen, in 1720, says: "This gland, beyond doubt, serves also to moisten the neighbouring parts; but, because it is very large, there is an apparent reason why it should have rather large excretory ducts, or one at least very conspicuous, which yet hitherto has not been discovered."

Morgagni is undecided whether or no the gland has a duct. He describes vesicular cavities in enlarged thyroids, and these he correctly supposed to be the normal vesicles ("natural cavities") distended by the accumulation of their secretion.

He is inclined to think that there must be a duct opening into the pharynx or the trachea.

Santorini fails to find a duct, but still thinks that the thyroid gland may be forced to expel its secretion by the contraction of the overlying muscles and other causes.

Haller, in his textbook, written in 1776, after discussing the anatomy of the gland and detailing the fruitless attempts to discover an efferent duct, says: "Alii Cl. viri, cum penitus de inveniendo ductu desperassent, ad aliam omnino utilitatem se converterunt. Liquorem peculiarem in ea glandula parari, qui receptus venulis sanguini reddatur, quæ lienis et thymi fit utilitas, ipse Ruyschius autumavit."

Thus, in the year 1776, we have the thyroid, the thymus, and the spleen classed together as glands without ducts, which manufacture a special fluid, which is received into the veins, and so returned to the general circulation. This, so far as it goes, and, so far, at any rate, as it refers to the thyroid, is not far different from the modern conception.

Although from this time on the glandular nature of the thyroid was universally conceded, and there was much speculation as to the precise mode of secretion and the elimination of the product from the vesicles into the circulation, yet the active function of the secretion itself was for a long period not the subject of any serious inquiry, and, indeed, the possibility of its being of any great importance in the economy was scarcely suspected. Thus, Cruveilhier, in 1834, states that the use of the secretion of the thyroid is unknown, and about this time Sir A. Carlisle supposed that the gland forms a protection to the delicate organs of the voice, against the variations of the external air.

In 1844 Simon put forward a very interesting theory in regard to the function of the thyroid, all the more interesting as it has quite recently been revived. Simon considered that the thyroid exercises a regulatory function on the blood-supply to the brain, exerting also its secretory function in an alternating manner with the substance of the brain. "What diversion is to the stream of blood viewed quantitatively, alternative secretion would be to the composition of the blood viewed qualitatively; and I should conceive that the use of the thyroid gland, in its highest development, may depend on the joint exercise of these two analogous functions. I should

suspect not only that the thyroid receives, under certain circumstances, a large share of the blood which would otherwise have supplied the brain, but also that the secretion of the former organ bears some essential relation (which chemistry may hereafter elucidate) to the specific nutrition of the latter; that the gland—whether or not it appropriates its elements in the same proximate combination as the brain does—may, at all events, affect in a precisely similar degree the chemical constitution of the blood traversing it, so that the respective contents of the thyroid and cerebral veins would present exactly similar alterations from the characters of aortic blood. Finally, I should suppose that these actions occur only or chiefly during the quiescence of the brain, and that when this organ resumes its activity, the thyroid may probably render up again from its vesicles to the blood, in a still applicable form, those materials which it had previously diverted from their destination."

Writing a few years later (1849–1852), Handfield-Jones still thought it necessary to criticize adversely the various ancient theories which supposed the thyroid to bear some functional relationship to the larynx. He says that there seems no doubt that the relative position of the thyroid to the larynx is quite unimportant, so far as the function of the organs is concerned. This is borne out by the variations of its site, which occur in birds, and by the results of morbid action, since prodigious goitre does not induce disease of the larynx, except in a mechanical way—*i.e.*, by injurious pressure.

Referring to Simon's theory, Handfield-Jones remarks, "It is the only one yet promulgated which can be said to be even probable." He does not, however, declare himself an adherent to the theory, of which, in fact, he offers several criticisms.

K. Extirpation Experiments upon Mammals

The earliest extirpation experiments upon animals appear to have been performed by Raynard. This observer reports that the treatment of goitre in dogs can be carried out just as in man. Complete removal of the thyroid was successfully carried out in dogs of medium age and in old dogs, but in young animals death occurred within a few days. The post-mortem examination did not reveal the cause of death.

Astley Cooper gave some account of the structure of the thyroid and extirpated the gland from two pups ten weeks old. The animals recovered after suffering from stupidity and malaise. The animals were killed very soon after the operation.

Moritz Schiff, during the years 1856, 1857 and 1858, carried out a series of thyroidectomies upon various animals. Some rabbits, some rats, some fowls, and some dogs survived the operation, but several dogs, a cat, and a rat died after some days.

The earlier results of Schiff were apparently read before the Royal Academy of Science in Copenhagen and then buried in a work on the formation of sugar in the liver. It is not surprising that they remained unnoticed for many years. Cretinism had long been recognized, and in 1874 Gull described the condition which Ord, in 1878, called "myxœdema." In 1882 the Swiss surgeons noted the symptoms of "cachexia strumipriva," or "operative myxœdema," after operations for goitre in the human subject.

After an interval of a quarter of a century Schiff was led by the observations of Kocher and Reverdin in Switzerland to take up the problem again. In 1884 he recalled his earlier experiments of 1856–1858, and published the results of a new series of investigations. In the rat and the rabbit, thyroidectomy was not followed by any serious result. In the dog and cat, however, complete removal was fatal. He gives an admirable account of the nervous symptoms after removal of the thyroid in the dog, and states that these may be avoided by a previous graft of the thyroid of one dog into the abdominal cavity of another. Other symptoms noted by Schiff were general malaise, arrest of growth, and in two cases œdema.

It must be noted that some of these symptoms, particularly those of a nervous nature, are at the present time attributed to loss of parathyroid tissue which must have occurred when the thyroid was extirpated in dogs and cats.

Wagner and others confirmed Schiff's observations, and it has been stated that the first-named author found an increased response in the nerves to galvanic currents after removal of the thyroid (and parathyroids) in cats.

Horsley was the first to operate on monkeys. He states

that a week after the operation fibrillary twitchings of the muscles were noted, and that these ceased on voluntary movement. The animal then became "cretinoid." There was a "myxœdematous" condition of the subcutaneous tissues. The tremors were relieved by keeping the animal warm. According to Horsley, there were swellings of the skin of the face and abdomen, due to the infiltration of the tissues by mucin. The salivary glands became enormously hypertrophied and the parotid gland produced large quantities of mucin.

We are not concerned in this place with the nervous symptoms described by Horsley, but it may be observed in passing that so far as I am aware no subsequent observer has been able to obtain these "myxœdematous" symptoms in monkeys or in other animals. Horsley gives no detailed protocols of his experiments.

Removal of the thyroid from different animals was carried out by a number of observers during several succeeding years. The majority of these confirmed the general views of Schiff as to the effects of total extirpation of the thyroid. It must be remembered that at this period the possibility of a separate functional importance of the parathyroids was not suspected, so that while in dogs, cats and monkeys thyroids and parathyroids were always removed together, in the herbivora the two external parathyroids were left behind in what was called "total thyroidectomy." For, although the external parathyroids were discovered by Sandström in 1880 and by Baber in 1882, it was not until Gley rediscovered them and demonstrated their functional importance in rabbits that experimenters gave them due consideration. This was in 1891.

Following Horsley's work came a series of papers by numerous authors. These all supported the view of Schiff as to the effects of total extirpations of the thyroid. But some were inclined to deny the supreme importance of the thyroid in the animal economy and attributed the untoward symptoms recorded by other workers to injury to nerves, reflex action, and similar causes. Munk's observations are specially interesting in view of the results obtained by some more recent observers (*vide infra*). He came to the conclusion that the chronic disturbance of nutrition in thyroidless animals is nothing more than "gefangenschaftkachexia" which may

often be observed in unoperated animals. He states that out of four monkeys operated on in England one was sent to him as "myxœdematous." The animal had nothing more than an ill-defined facial swelling, probably due to a carious tooth, and an intermittent paresis of a fore limb. The animal was, according to Munk, otherwise in good health and lived for ten months after the operation. Munk insisted that although removal of the thyroid is a dangerous operation, it does not follow that the thyroid is absolutely essential to life. And this statement must be admitted as justifiable, even if the survivals are due to thyroid or parathyroid tissue which is so placed that it cannot be removed. It will be necessary to return to this point.

The further account of Gley's work, as well as that of Vassale and Generali and Kohn, will be found in the section on the physiology of the parathyroids.

The experiments of Vincent and Jolly may be briefly recalled so far as they relate to the general question of extirpation of thyroids and parathyroids, and more particularly in regard to the effects alleged to be due to elimination of the function of the thyroid. On these points the general conclusions were: "Neither thyroid nor parathyroids can be considered as organs absolutely essential for life. Rats and guinea-pigs do not seem to suffer at all as the result of extirpation. Monkeys show only transient nervous symptoms. Dogs, cats, foxes and prairie wolves frequently suffer severely and die. On the other hand, badgers do not appear to be affected by the operation.

"In no animals, not even in monkeys, have we been able to induce any swellings of the subcutaneous tissue, which is the most striking feature of myxœdema in the human subject. We think, therefore, that the pathology of myxœdema must be more complex than simple thyroid insufficiency." [1]

Several previous observers from Schiff onwards had noted the fact that thyroidectomy in dogs and cats is by no means always fatal. At the same time there has been a tendency to disregard the exceptions, and, when any explanations have been offered it has been suggested that they are due to parathyroids having been overlooked at the operation, or to the existence of accessory thyroids. Munk (*vide supra*) indeed is among

[1] On other points discussed in these papers the present writer has changed his opinion. This applies to the change of parathyroid into thyroid.

the few observers who have laid due stress upon the cases of survival. This observer, as we have seen, admits that removal of the thyroid is dangerous, but not that the gland is an organ essential to life. We cannot assail the logic of the position that an organ which may frequently be removed with impunity is not "essential to life" and the results obtained by Vincent and Jolly forced them to extend the observation so as to include not only the thyroid but also the parathyroids.

According to Noël Paton, a "contention that the removal of the parathyroids does not produce the train of symptoms terminating fatally, must in the light of the work of other investigators be explained as due to a failure to remove all the parathyroid tissue." Now, in the case of rabbits, Paton quotes Pepere to the effect that accessory parathyroids are nearly always found in the thymus in rabbits. So that in rabbits parathyroidectomy is only fatal in the few animals which happen not to have any parathyroid tissue in the thymus.

In the monkeys employed by Vincent and Jolly no symptoms of myxœdema were observed when thyroids and parathyroids were completely removed. These results differ from those obtained by Horsley (*loc. cit.*), Murray and Edmunds, who state that it is possible to induce myxœdema by operation. This may be compared with the results obtained by Munk (*vide supra*) and Kishi. The last named only recorded one death out of six. Our animals were subject to catarrh, and one died of some laryngeal affection, and it seems probable that as in the case of other animals, removal of the thyroid gland leaves monkeys in a condition in which they are less capable of resisting disease. There is no reason to attribute death, when it occurred, to loss of thyroid or parathyroid. The animals were in good health, were active, and but for loss of weight showed no ill effects.

Carlson and Woelfel report that myxœdema does not develop in thyroidectomized rabbits, at least in seven months, nor in the monkey in several months.

In some groups of animals age seems to make a great difference to the results both of thyroidectomy and of "complete" thyro-parathyroidectomy. Sutherland Simpson found that removal of the thyroid with the contained internal parathyroids in thirteen adult sheep and sixteen lambs from seven to eight months old, led to practically no ill effects (see Fig. 88). As a

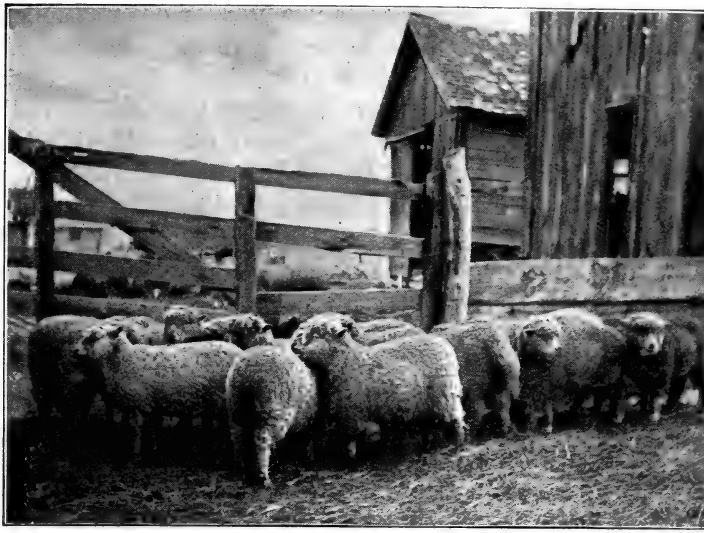


FIG. 88.—Photograph of group of thyroidectomized sheep taken five months after operation (after Simpson—*Quart. J. Exp. Physiol.*).

result of a similar operation, three lambs about two months old became "typical cretins."

The complete operation (thyro-parathyroidectomy) in four young lambs (five to seven weeks old) resulted early in acute and fatal tetany. Removal of the two external parathyroids

FIG. 89.—Photograph of cretin lamb about one year old, and of normal lamb of eleven months (after Simpson—*Quart. J. Exp. Physiol.*).

from the three cretins when about one year old was followed by only slight symptoms. According to Simpson, age is an important factor with regard to the effects of both thyroidectomy and parathyroidectomy. The "typical cretins" of Simpson are described as "small and stunted, with broad faces and rickety limbs. The wool was coarse, but did not tend to fall out." In some of the young animals (cats and dogs) operated on by Vincent and Jolly interference with growth was very striking, but the other "cretinoid" symptoms were absent.

Basinger in 1916 carried out an extensive research on thyroidectomy in rabbits. Out of 140 animals operated upon "typical cretinism" was produced in 86. The experiments were carefully controlled as to feeding, and selection of subjects and normals from the same litters. The thyroidectomy was performed at the age of 2 to 3 weeks when the body weight was about 175 gms. Great care was taken to remove all thyroid tissue, leaving the external parathyroids intact, but it was subsequently found that in a considerable proportion of cases minute bits of the gland had been left behind and prevented the onset of cretinism. In different litters the proportion of successful results varied from 25 to 90 per cent.

About two weeks after the operation the onset of cretinism was detectable. The hair became dryer than normal, did not lie smoothly and could easily be pulled out. Retardation of growth was noticeable as early as the third week; it was greatest from the eighth to the twelfth weeks. By the end of the tenth week the average weight of the cretins was 750 gms., while that of the controls was 1400 gms. The posture of the cretins was typical. The bones were short and the muscles of the limbs too weak to support the body weight. The bones showed a pseudo-rickety condition (Hofmeister's "chondrodystrophia thyreopriva"). The skin became increasingly dry and scaly and finally eczematous. The typical "pot belly" seen in human cretins developed. No evidence of the typical myxœdema such as is seen in human cases was observed. Neither did chronic, progressive cachexia appear in any of the cretins, although they were kept for a year.

Transfusion of normal blood serum into the cretins had no apparent effect on their condition. Some improvement, however, resulted from transfusion of serum from thyroid-fed

rabbits. Administration of desiccated thyroid gland substance markedly relieved the symptoms but failed to bring about a complete cure. The cretins proved more susceptible than normal rabbits to the toxic action of thyroid feeding.

It seems clear from the experiments of Sutherland Simpson and others that in young animals removal of the thyroid (one or more parathyroids being left behind) will bring about a condition resembling cretinism in the human subject. In older animals symptoms may not be observed, but thickening and dryness of the integument with a tendency to loss of hair and wasting followed by adiposity have been described. It is stated that there is loss of muscular tone, and that regeneration of tissues is slower than normal. There may be anæmia. The body temperature is low; the power of heat regulation is diminished and the animal becomes poikilothermic; the sexual functions are interfered with. It has been stated that the limit of assimilation of carbohydrates is raised. "The nervous system is markedly affected, dulness and apathy being prominent symptoms. Many nerve-cells, especially those of the cerebral cortex, exhibit a shrunken appearance, and present a strong contrast with those of the normal animal (Schäfer). A myxœdematous condition of the skin has been described by some authors, but the present writer has never seen this (*vide supra*).

Thyroidectomy in the amphibia interferes with the normal metamorphosis, and retards or completely stops growth and ossification of bone. The operation does not appear to hinder the development of the gonads.

Several observers have reported a diminution in the alexins and opsonins in the serum after removal of the thyroid.

L. The Mechanism of the Thyroid Secretion

It used to be asserted that the secretion of the thyroid gland passes, not directly into the blood-stream, but indirectly by means of the lymphatics. But more recent investigations have rendered this theory very doubtful.

Asher and Flack utilized the observation of Cyon that the excitability of the depressor nerve is increased by the action of thyroid substance. They believe that the thyroid furnishes an internal secretion which increases the excitability of the

depressor nerve, and augments the effect of adrenin upon the blood-pressure. According to these authors the secretory nerves to the gland are the laryngeal nerves.

More recent investigation seems to point to the sympathetic as the origin of the secretory fibres to the thyroid. Rahe, Rogers, Fawcett, and Beebe find that stimulation of vessels with the accompanying nerve filaments causes a diminution in the amount of iodin contained in the gland. These authors conclude that the thyroid is at least in part under nervous control, and that its physiologically active substance is discharged into the circulation in response to a nerve stimulus.

The view that the sympathetic fibres are true secretory nerves to the thyroid is supported by the observations of Cannon and Cattell upon the electrical response of the gland during activity. (See p. 33.) Control by the sympathetic suggests that adrenin may stimulate the thyroid to increased activity, and this was proved to be the case by intravenous injection of adrenin, and by stimulation of the adrenals through the sympathetic nerves. By continuous stimulation (fusion with the phrenic) of the cervical sympathetic a condition resembling exophthalmic goitre was produced. It seems possible that the thyroid (like the adrenal) has an emergency function, which would increase the rate of metabolism and augment the efficiency of the adrenin secreted simultaneously.

Rogoff tried to detect in the blood coming from the thyroids of three dogs a physiologically active secretion, tested by feeding tadpoles with the dried blood. The number of experiments recorded is not sufficient to warrant us in drawing any very definite conclusion.

M. The Chemistry of the Thyroid

The most striking feature of the thyroid gland from a chemical standpoint is the constant presence in it, under normal conditions, of measurable amounts of iodine.

The following elements have been stated to be present in the thyroid: carbon, hydrogen, oxygen, nitrogen, sulphur, phosphorus, sodium, potassium, calcium, magnesium, silicon, arsenic, fluorine, chlorine, bromine, and iodine. It was in 1854 that Macadam found iodine in food plants, but it was not until 1895 that Baumann discovered the presence of this

element in the thyroid. It is now generally recognized that the vertebrate thyroid invariably contains iodine. The percentage varies from 0·01 to 1·16 for dried glands. Other mammalian tissues do not contain more than about 0·001 per cent.

There are now three reliable methods for the detection and estimation of iodine: those of Bourcet, Hunter, and Kendall. The two latter with 0·5 gramme of material will detect the presence of 0·001 per cent. of iodine with accuracy. Utilizing these methods, Cameron finds that iodine is an invariable constituent of all marine Algae (0·001 to 0·7 per cent. of dried tissue). Land plants contain much less. All marine animals contain iodine. In vertebrates this is found practically entirely in the thyroid. Small amounts of the other halogens are also found.

The relative amount of thyroid tissue seems to increase as we ascend the scale of evolution. But the iodine content does not increase in a corresponding degree. It would appear that in cattle both thyroid tissue and iodine content are greater in the female than in the male. In regard to age, the maximum iodine content in the human subject is found between 40 and 60 years. The lowest figures are obtained from subjects under 15. According to Seidell and Fenger there is a seasonal variation in the iodine content of sheep, pig, and ox thyroids. Thus, the percentage between June and November is usually from two to three times as great as that between December and May. Diet appears to be insufficient to explain the seasonal variations. They are probably due to metabolic changes due to temperature.

But the most important factor in the causation of variations in the iodine content of the thyroid is undoubtedly diet. The administration of iodine as iodides rapidly raises the iodine content of the thyroid. From the time of Baumann numerous observations have shown that the amount of iodine in the thyroid depends on the amount of this element in the normal diet. Thus the thyroids of the herbivora have more iodine than those of the carnivora. Sheep fed largely on seaweed show a large amount of iodine in the thyroid. In an ordinary human diet the thyroid iodine is obtained from fish, molluscs, milk, eggs, wine, etc.

It is probable that the iodine of the thyroid is chiefly con-

tained in the colloid substance, though there is some evidence that the cells of the vesicles also contain a certain amount.

In algae most of the iodine is in soluble organic (non-protein) combination, a trace only being present as iodide. Drechsel found an iodo-amino-acid in the skeleton of a coral, which was later identified as di-iodo-tyrosin. Dibrom-tyrosin is also found in corals and sponges. It is said that *p.*-iodophenyl-alanine is present in sponges.

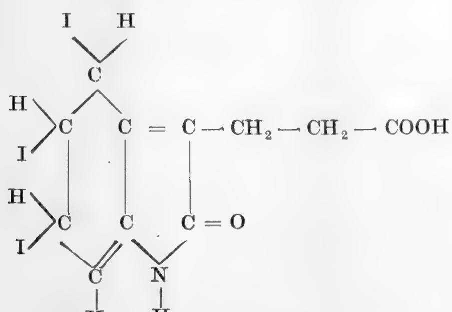
None of these can be isolated from the thyroid. In the gland most if not all the iodine is in organic combination. Some observers state that there is a small amount of iodide present. Baumann boiled thyroid glands with sulphuric acid. The residue was extracted with alcohol and evaporated to dryness. The product was called thyroiodin or iodothyrin. It contained 10 per cent. of iodine, and amounted to about 4 per cent. of the total weight of the dried thyroid. It has been found that Baumann's product was not of a constant chemical constitution, and it has been suggested that the iodine compound present was iodotryptophane. Various other thyroid preparations have been made and have been put forward as the "active principle" of the thyroid gland. Iodothyroglobulin (Oswald) is possibly a definite compound and exists as such in the thyroid gland.

In 1919 Kendall announced the isolation of a definite crystalline iodine compound which he calls "thyroxin." His method of isolation is given as follows: "The fresh thyroid glands are hydrolyzed in 5 per cent. sodium hydroxide in a nickel kettle, the fats are removed by rendering the sodium soap insoluble, and the clear alkaline filtrate is cooled and acidified. The acid insoluble constituents containing practically 100 per cent. of the thyroxin present are filtered off. This material is redissolved in sodium hydroxide and reprecipitated, using hydrochloric acid. The precipitate is now air-dried and is dissolved in 95 per cent. alcohol. The excess hydrochloric acid which remains in the air-dried precipitate is neutralized with sodium hydroxide until it is almost neutral to moistened blue litmus paper. A heavy, black, tarry precipitate forms, which may be removed by filtration. The alcoholic filtrate is treated with barium hydroxide by adding a hot, very concentrated aqueous solution of the hydroxide to the alcohol, and refluxing. The treatment with barium removes some

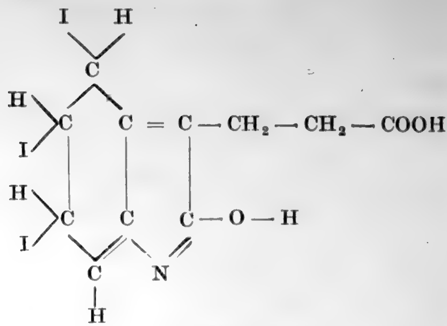
heavy dark impurities. A small amount of sodium hydroxide is added to the filtrate and carbon dioxide is passed through the solution. The barium and sodium carbonate are removed by filtration, and the alcohol is distilled. The last traces of alcohol are removed by heating in an evaporating dish. The aqueous residue is now acidified with hydrochloric acid. The precipitate is dissolved in alkaline alcohol, carbon dioxide is passed through the solution, the precipitated sodium carbonate is removed, and the alcohol is evaporated. The last traces of alcohol are removed by heating on a water bath and the solution is allowed to stand. The monosodium salt of thyroxin will separate at this point. The yield is not quantitative, and it must be further purified by dissolving in alkaline alcohol, passing in carbon dioxide, distilling the alcohol, and allowing the monosodium salt to crystallize a second time. This may then be precipitated from an alkaline alcoholic solution by the addition of acetic acid. Re-solution in alkaline alcohol and precipitation with acetic acid for five or six times removes the impurities and will yield thyroxin containing the theoretical percentage of iodine."

Kendall states that he has obtained 33 grammes of thyroxin from 6,550 pounds of fresh thyroid.

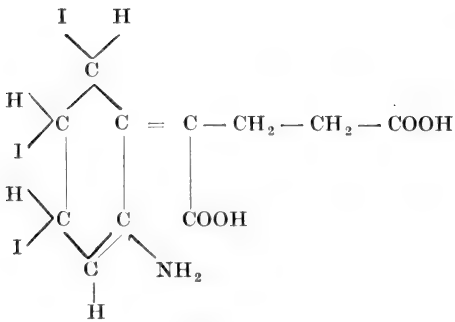
Thyroxin is said to be 4,5,6, tri-hydro,—4,5,6, tri-iodo—2 oxybetaindolepropionic acid. It exists in three forms: (1) the keto form with the carbonyl group adjacent to the imino, (2) A tautomeric enol form, and (3) A form with an open ring structure (cp. creatine and creatinine). It can be regarded as a derivative of tryptophane. According to Kendall the third form is that in which iodine occurs in the body.



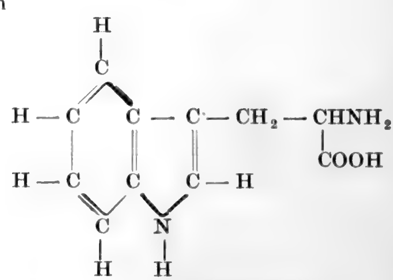
(1) Keto form



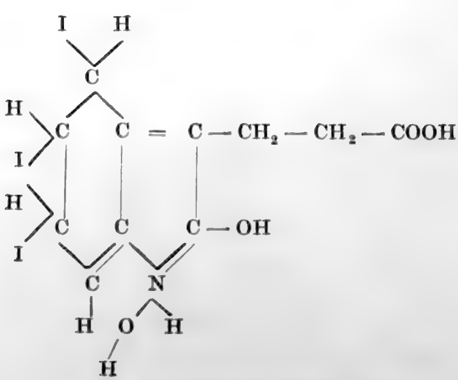
(2) Enol form



(3) Open-ring form



Tryptophane



(4) Amino-hydrate form

The change to the open ring form is effected easily in presence of certain products of hydrolyzed protein which contain the indole nucleus.

(1) The keto form (formula 1) crystallizes in needles and is tasteless and odourless. It is found in the keto form in acid solution. It is insoluble in organic solvents unless they are acid or basic. It is soluble in alcohol in the presence of mineral acid or an alkali. It is not destroyed by heating. The melting point is 250° C. Mol. Wt. = 585, and empirical formula $C_{11}H_{10}O_3NI_3$ (cf. tryptophane $C_{11}H_{12}O_2N_2$). It is amphoteric. It can yield a sulphate, a hydrochloride, a ureide and an acetyl derivative. It gives also mono- and di-basic salts, but these are so easily decomposed that they cannot be obtained in a pure form.

(2) The enol form (formula 2) exists in alkaline solution. It may be prepared by hydrolysis in the cold of the ammonium salt, solution in pyridine and addition of water, when it separates out in needles (melting point 204° C). It is easily soluble in anhydrous or aqueous pyridine and quinoline and in formic acid. It is easily changed into the keto form.

(3) The open-ring form (formula 3) is obtained by adding sulphuric acid to an alkaline watery solution of thyroxin. The precipitate which is formed is suspended in water and boiled. Thyroxin is then thrown down in long crystals (melting-point 225° C.). It is soluble in alcohol, changing in solution to the keto form.

A fourth (amino-hydrate) form (formula 4) may be obtained from an alkaline solution of thyroxin by heating and adding 10 per cent. ammonium chloride. Fine crystals with a melting-point of 216° C. separate out. If these are suspended in water acidified with formic acid and boiled, the crystals are changed into the open-ring form.

If nitrous acid be added to an alcoholic solution of thyroxin or to a suspension in water in presence of hydrochloric acid a yellowish colour is developed which, on addition of ammonia, changes to deep red. This reaction serves as a test for thryoxin.

Thyroxin is more susceptible to reduction than to oxidation. Zinc and other metals in acid or alkaline solution split off iodine and break up the nucleus. Mild oxidizing agents have no effect, stronger ones break down the molecule. Thyroxin is unstable in sunlight; iodine is split off as hypoiodous acid and

subsequently as free iodine. The iodine content is 65 per cent. It is said that a small quantity has already been synthesized.

Thus it appears that two definite compounds containing iodine have been separated from thyroid tissue, a globulin (iodo-thyro-globulin) which exists as such in the gland, and a derivative of tryptophane (thyroxin) obtained as a cleavage product and containing 65 per cent. of iodine. The evidence before us points to thyroxin as one of the active compounds of the internal secretion of the thyroid gland. But it is too early to affirm that it is the only active compound.

N. Physiological Actions of the Thyroid Secretion

Kendall claims that thyroxin produces all the effects of thyroid both physiologically and therapeutically. Thus it is found as useful in myxœdema as other thyroid preparations.

Thyroxin shows a curious delay in its action. Successive daily administration may bring about death, but a single injection even of enormous size produces no effect. 1 mg. of thyroxin in an adult weighing 150 pounds will increase the metabolic rate 2 per cent.

Kendall suggests that in the normal animal organism thyroxin is not fundamentally essential to life. This agrees with the results of extirpation experiments described above, and further is in accordance with the emergency theory of Cannon (*vide supra*). It is suggested that thyroxin is a catalyst, and that its function is to increase the rate of the fundamental chemical reactions of the body.

Intravenous injection of thyroid extracts or of thyroid preparations produces a temporary fall of blood-pressure. This effect is in all probability not a specific one. It is probably the same kind of fall as is produced by the injection of extracts of most organs and tissues in the body. The fall is due to a dilatation of peripheral vessels throughout the body. We have no reason to believe that this effect on blood-pressure has any bearing on the question of the internal secretion of the organ. The probable nature of the substance has been discussed above (p. 25).

Gudernatsch and others have observed that feeding tadpoles with thyroid substance will cause precocious differentiation, while growth is suppressed. The tadpoles begin to

undergo metamorphosis a few days after the application of the thyroid and long before the control animals do so. The reaction was supposed to be a delicate test for the presence of physiologically active thyroid substance.

The reaction however does not appear to be a specific reaction of thyroid substance since it has been found to occur after administration of iodides and iodized blood-serum. Kendall states that the action on metamorphosis (which occurs with small doses of his "thyroxin") is not due to the organic nucleus, but is due to the iodine in the molecule, which breaks off as hypoiodous acid (HI O).

Carrel states that tissues grown *in vitro* increase several times as rapidly in the presence of thyroid substance as in its absence.

The administration of thyroid substance and of iodide to animals has yielded some interesting results. In determining the effect on gross weight most of the earlier observations were made on adult animals. In regard to the effect on growth in young animals, some observers have noted an increase in the rate of growth, others a decrease, while still others have recorded that no distinct effect was produced. Cameron was the first to use a dose based rigidly on and bearing a constant ratio to the body weight of the animal at the time of administration. He has found, as the result of a series of very careful experiments, that continued small doses of desiccated thyroid gland administered to young white rats produce (*a*) a definite and invariable decrease in rate of growth; (*b*) hypertrophy of the organs concerned with increased metabolism—heart, liver, kidneys, adrenals, etc. (confirmatory of Hoskins and Herring); (*c*) disappearance of fat (confirmatory of Hoskins and Herring). The decrease in rate of growth is proportional to (*a*) the amount of thyroid administered and (*b*) the iodine content of the gland given. The hypertrophy varies with the dose and length of time during which it is administered, and appears also to be proportional to the iodine content of the dose. Sodium iodide given in quantities varying from amounts equal in iodine content to the thyroid doses to amounts a hundred times as great produces no effect on growth rate and no hypertrophy. The effects produced are not due to protein feeding, autolytic products, or any similar cause, but specifically to thyroid tissue, or some constituent of it. Both thyroid and iodide

feeding increase the colloid in the thyroid. Thyroid feeding inhibits the growth rate of the thyroid while iodide does not. Similar effects were obtained in experiments upon rabbits. Since among all the organs and tissues of the body thyroid alone produces a definite effect and since iodide does not produce this effect, it is suggested that decreased rate of growth, hypertrophy of liver, heart, kidneys, and adrenals, and relatively decreased thyroid may be used as tests for preparations alleged to be the essential thyroid secretion. According to more recent observations of Cameron, Kendall's thyroxin produces effects similar to those of thyroid when given by the mouth. But quantitatively, compared on a basis of iodine content, the effects of thyroxin are distinctly less than those of desiccated thyroid. This is probably due to bacterial decomposition ; thyroid acts as a shield. The hypertrophy of heart and lymphatic tissue resembles that observed in cases of hyperthyroidism.

Many attempts have been made to induce symptoms of exophthalmic goitre by means of the administration of thyroid substance to animals. It is doubtful whether a condition strongly resembling Graves's disease has ever been brought about by such methods. But there can be little doubt that definite toxic effects can be produced by thyroid feeding. These are loss of body weight, gastro-enteritis, and diarrhœa, rather than tachycardia, nervousness, and exophthalmos. Kendall believes that in order to get "hyperthyroidism" we must have thyroid and adrenal cortex acting together. It has not yet been determined how far the toxic symptoms just described are due to iodine quâ iodine.

O. The Effects of Thyroid Gland, and Preparations made from it, upon Metabolism

Many years ago it was observed that myxœdematous subjects, when treated with thyroid, suffered loss of weight due to reduction of fat and water. Since then various thyroid preparations have been employed to reduce obesity.

When systematic metabolism experiments were carried out it was usually found that thyroid causes an increase of nitrogen in the urine, showing increased protein metabolism. The same or similar results were obtained with "iodothyrin" and

"thyreoglobulin," in the case of the latter the effect varying with the amount of iodine present.

According to Cramer the administration of thyroid practically abolishes the store of glycogen in the liver. The increased katabolism of protein and fat is secondary to increased mobilization of the glycogen in the liver. According to Frontali and Hunter there is a very great elimination of creatine in sheep and dogs after removal of both thyroids and parathyroids. Kendall's thyroxin produces a notable effect on metabolism. The statement has been made that certain amines derived from proteins have an effect on metabolism of the same character as that brought about by thyroid substance.

P. Transplantation of the Thyroid Gland

A large number of transplantation experiments have been performed, with very variable results. Many different methods and many kinds of animals have been used. In some cases rapid degeneration and loss of the grafted organ has occurred. In others apparently the tissue has remained alive and active for months.

When the gland from one animal is grafted into another of different species (heteroplastic transplantation) the operation is always unsuccessful. When the thyroid from one animal is grafted into another of the same species (homoioplastic transplantation) the proceeding is perhaps sometimes successful. When a piece of thyroid is grafted on to various parts of the same animal (autoplastic transplantation) the operation is quite likely to be successful. The grafts frequently "take" and are said to remain in functional activity for long periods. When transplantation takes place into nearly related individuals of the same species (syngenesioplastic transplantation, Loeb) the results obtained are intermediate in point of success between those obtained by auto- and homoioplastic transplantation. The transplanted gland lives for a certain time, but subsequently becomes absorbed by lymphocytal infiltration.

By the vessel suture method of Carrel and Guthrie the thyroid may be removed from its proper position and replaced in the neck. It would appear that by this method the autoplastic form of transplantation is the only one which has been successful. One case of homoioplastic grafting has been recorded as successful in the human subject.

Q. The Relationships between the Thyroid Gland and the Reproductive Functions

In the case of women some kind of relationship between the thyroid gland and the functions of reproduction has been recognized for a very long time. Thus it has been known that the gland is relatively larger in women than in men, and the conspicuousness and relatively large size are more marked after puberty and during the periods of menstruation and pregnancy. We know from observations on cretins and upon thyroidless animals that the proper growth and development of the sexual organs depends on the functional integrity of the thyroid gland. It is stated that sexual intercourse both in men and in women entails increased activity of the gland and gives rise to an increase in volume. McCarrison believes that married men and women under forty years of age owe their superior physique to the maintenance of thyroid activity which marriage assures.

The ovaries are believed to exert an inhibitory action on the thyroid gland, so that the latter becomes over active after castration. This hyperactivity is revealed by an increase in the amount of colloid matter. This is also put forward in explanation of the large number of cases of exophthalmic goitre which occur after the menopause. Bearing in mind the important though ill-understood relation between the adrenal cortex and the reproductive organs it seems probable that the relations of the thyroid to the sexual functions will only be fully understood when the functions of the adrenal are better known.

R. The Functions of the Thyroid Gland

The evidence before us points to the conclusion that the thyroid gland provides a substance or substances which aid in the growth, morphological differentiation, and metabolic processes of the body. One of these substances seems to be an iodized amine—thyroxin. Most of the activities attributable to the active principle or principles are in the direction of katabolism, though, according to some authorities, there are indications of the existence of an anabolic principle. It is not known whether there are two separate active substances—one anabolic, the other katabolic. The secretion of the active

principle or principles is probably under the control of the sympathetic. Whether the influence of the active material is direct on the tissues themselves, or indirect through the nervous system, is still doubtful. The thyroid is not equally important in all groups of animals. Adult herbivora can live in good health without a thyroid while the carnivora under such conditions will frequently suffer severely and die.

Kendall regards the action of the thyroid substance as that of a catalytic agent. The substance does not alter the character of the fundamental reactions but increases their rate.

The antitoxic action of the thyroid gland depends in all probability on its metabolic function. The slowed changes of material in the body after removal of the thyroid will diminish the amount of alexins and opsonins and so render the animals more liable to infection. Regarding the perplexing problem of the iodine, it seems wise to assume provisionally that this element, in certain organic combinations, is of service as a catalytic agent in aiding or accelerating the fundamental metabolic processes of the body. We may also assume that the thyroid has for its function the utilization of the iodine in the diet to build up the particular compound or compounds which are necessary. Kendall believes that the essential part of the active substance is the NH_2COOH group, and that the iodine modifies the action, but is not essential. But he has not yet succeeded in preparing the active nucleus without iodine.

S. **Extirpation Experiments upon the Parathyroid Glandules**

The external parathyroids were discovered by Sandström in 1880. But it was not until their rediscovery by Gley in 1891, and the description of the internal parathyroids by Kohn in 1895, that extirpation experiments could be carried out with due regard to anatomical considerations.

Vassale and Generali removed all four parathyroids from nineteen animals—ten cats and nine dogs—leaving the thyroids intact. Of the ten cats, nine succumbed within ten days, most of them at about the fifth day after the operation, after presenting a typical train of symptoms. There were fibrillary twitchings, muscular spasms, psychical depression, stiff and

tottering gait, loss of appetite, tachycardia, rapid emaciation, and lowering of body temperature. One of the cats, operated upon on January 5, 1896, was still alive in March of the same year, but was much emaciated and in a state of chronic cachexia. The nine dogs all died within eight days, mostly on the third or fourth day after the operation. They were as a rule in good health the day after the operation, but began to show symptoms on the second or third day, and then rapidly died, after manifesting a variety of morbid symptoms. These were psychical depression, muscular tremors, paresis of the muscles of mastication, trismus, rigidity of the hind-limbs, uncertain gait, general muscular feebleness, and convulsions. There were also anorexia and vomiting, palpitation and dyspnœa. The urine was scanty and sometimes contained traces of albumin.

The symptoms after removal of the four parathyroids were, as Vassale and Generali pointed out, analogous to those observed after removal of thyroid and parathyroids, an operation which had been so often unwittingly performed since the time of Schiff. The Italian observers did not note very marked convulsions; these only occurred near the fatal termination. The predominating features were, in fact, expressive of diminution of the excitability of the nerve centres; there was, in fact, a rapidly fatal paralysis. The autopsy usually revealed nothing abnormal in the lung; spleen and kidneys were congested. The nervous system was normal with the exception (in some cases) of a certain degree of anæmia.

The authors were satisfied that the fatal issue was not due to complications arising from the operation itself, or to lesions of the thyroid or the surrounding nervous structures. In most cases the wound was in process of healing by first intention; in the cats there was very often complete cicatrization. Vassale and Generali state that the thyroid suffered little or not at all in the operation. In some cases the thyroid left behind possessed no colloid in its lymphatic spaces. They were surprised to find that death supervened in a shorter time than after removal of both thyroids and parathyroids.

In their second communication Vassale and Generali recorded a series of variations upon their original experiments. Thus they extirpated the two parathyroids of one side, with practically no effects. Removal of the four glands in two

operations (first those of one side, then those of the opposite side) showed that the first operation produced little or no result; the second operation proved rapidly fatal. Dogs could be kept in good health with only one parathyroid remaining, but the authors suspected that chronic symptoms might arise at a later period.

In a still later communication the Italian authors state that the tetany induced by thyroidectomy is less marked in old dogs than in young ones. The tetany is particularly well-marked in dogs, if, after removal of the thyroids, they are fed abundantly on a meat diet. If the animals are allowed to get into a condition of hunger, the tetany becomes much less noticeable.

Results similar to those of Vassale and Generali have been obtained by several observers.

The present writer, working in conjunction with Professor W. A. Jolly, encountered difficulties where, from previous study of the literature, they had not been led to expect them, and could by no means always induce death in animals by total parathyroidectomy.

From the writings of most authors it would appear to be a simple matter to remove, in some cases, the parathyroids leaving the thyroid intact, and in others the thyroid leaving the parathyroids *in situ*. Variations of these experiments would appear to be equally simple. Welsh, indeed, who worked with the cat, in which parathyroidectomy presents, perhaps, least difficulty, admits some difficulties in performing complete parathyroidectomy. According to Vincent and Jolly, Welsh has understated these. The obstacles in the way of success in this operation are mainly anatomical. The parathyroids are extremely variable in position. The external pair may, as a rule, be easily seen and removed, but the internal are, in the majority of cases, embedded deeply in the substance of the thyroid. When it is remembered how vascular thyroid tissue is, how slightly the parathyroid differs from it in appearance to the naked eye, and how this difference, slight as it is, entirely disappears when there is any bleeding, it will be seen that the operation of digging out the internal parathyroid is one of extreme delicacy. A further difficulty presents itself in the fact that there is a nodule of thymus also embedded in the thyroid lobe, frequently in close proximity to the internal parathyroid, resembling it on naked-eye examination, and

therefore easily mistaken for it in the course of the operation. Bearing all these difficulties in mind, the present writer and Professor Jolly did not hesitate to declare that, except in very favourable cases, where the internal parathyroid chances to lie near the surface of the thyroid lobe, the operation is an impossible one. The injury caused to the thyroid in endeavouring to excavate an almost invisible body from its substance, combined with the accompanying profuse hæmorrhage, may account for some of the deaths which other experimenters have attributed to parathyroid insufficiency. It will be obvious that the other operation—viz., to remove all the thyroid tissue, while leaving the parathyroids with their blood-supply uninjured—is still more difficult, and it was not attempted, though it was found possible in some cases to leave one or two external parathyroids.

The animals upon which the experiments were performed were cats, dogs, foxes, monkeys, rats, guinea-pigs, and rabbits.

Ten out of fifteen cats on which the total operation was performed, either at one or more times, died soon after, the respective periods of survival varying from three to thirty-four days. Five survived the operation. Of the animals which survived, three showed grave nervous symptoms as the result of the operation. The fourth, which was a young cat, ceased for a time to grow, while remaining otherwise perfectly normal. The fifth showed no symptoms. On what theory are we to account for the exceptions to the rule that death rapidly follows the complete operation? These exceptions are fairly numerous, and they have also formed a conspicuous feature of previous investigations. The presence of accessory thyroid or parathyroid tissue suggests itself as a probable explanation, but it must be borne in mind that a careful post-mortem dissection of neck, thorax, and even abdomen, failed to disclose such bodies.

The symptoms usually following the complete operation in the cat are as follows: The cat is perfectly well on the day following the operation; on the second day, there is usually a curious "paw-shaking" and some malaise. This is followed in rapid succession by tremors, stiffness of gait, and convulsions. Even in a quiescent state, the fore-legs tend to be flexed, while the hind-legs are extended, a position exaggerated during convulsions. Hallucinations are fairly common. Of symp-

toms not directly referable to the nervous system, conjunctivitis and respiratory catarrh were observed.

In the dog the following symptoms have been described: restlessness, anxiety, fibrillary twitchings, stiffness, and staggering gait, convulsions and fits of rapid breathing. This may reach 250 a minute. The rectal temperature is raised as a result of the muscular activity. Exhaustion may supervene and in extreme cases death. Emaciation is common and increased excitability of the peripheral nervous system is now regarded as pathognomonic of parathyroid tetany. The symptoms are extremely variable, so that it is difficult to judge of the effect of any curative agents.

The nervous symptoms required more careful consideration. The convulsive disturbances probably proceed from the central nervous system, since division of the motor fibres to any of the muscles will abolish them. The effect seems due to the condition of the spinal cord and does not depend upon any higher centres. As already stated the electrical excitability of the peripheral nerves is increased. It has been known for a long time that the phrenic nerve may be excited by the action currents of the heart, so that we get "cardiac respiration," in which the diaphragm contracts with each heart beat, a phenomenon very familiar to all who have carried out extirpation experiments on dogs. Hoskins and Wheeler have shown that there is also a marked increase in the irritability of the sympathetic nervous system.

Many theories have been brought forward to explain why removal of the parathyroids should give rise to the above symptoms. The two principal views are (1) calcium deficiency, (2) some toxic agent. Sabbatani and others had shown that soluble calcium salts diminish the excitability of nervous tissues. Utilizing this fact MacCallum has suggested that the pathology of tetany may consist in a deficiency of calcium in the body. An injection of soluble calcium salts into the circulation of an animal in tetany promptly checks the symptoms. The hyperexcitability of the nerves which is characteristic of tetany is due to some change in the blood. It has been shown by cross-circulation experiments, that if the leg of a normal animal is supplied with tetanic blood, this condition of hyperexcitability soon manifests itself in the nerves of the normal leg. The most powerful objection to the

calcium theory is that simply bleeding the animal and then replacing the blood shed by an equal amount of calcium free isotonic solution of sodium chloride (thus still further diminishing the calcium content of the tissues) also brings about prompt relief.

Various toxic agents have been suggested as being responsible for the phenomena of tetany. Among these are ammonia, xanthin, histamine, thymus secretion, inosinic acid, guanidine, and methyl guanidine. The only substance in this list which need be seriously considered is guanidine. In 1912, W. F. Koch made the very important discovery that methyl-guanidine is constantly present in considerable amount in the urine of parathyroidectomized dogs. In 1913 he definitely attempted to correlate this observation with the function of the parathyroid glands. He suggests that the parathyroid secretion is concerned with anabolic processes closely related with the building up of nucleins. This hypothesis has been developed more fully by Paton and his co-workers. They claim that guanidine injected into an animal will produce all the symptoms of tetany. They attribute this condition as found experimentally or clinically to an abnormal accumulation of guanidine in the body, which accumulation it is the duty of the parathyroid to prevent.

It has been supposed that the thymus produces a toxin tending to give rise to tetany, and that it is the duty of the parathyroid to reduce or destroy this.

The parathyroids do not contain any measurable amount of iodine. Other than this there is nothing to be said on the subject of the chemistry of the glandules. Attempts have been made to isolate the "active principle," but so far no very definite results have been obtained.

CHAPTER XIV

THE FUNCTION OF THE THYMUS

A. Comparative Anatomy and Development of the Thymus

1. NOTHING is certainly known of the thymus in the Cyclostomata.

In Elasmobranchs the thymus arises on each side as epithelial outgrowths of the dorsal gill-pockets. The number of clefts which give rise to thymus elements varies in different species, but it is probable that thymus buds originally arose from all the clefts.

A similar origin may be assigned to the thymus in Dipnoi, Ganoids, and Teleosts; but in these groups modifications occur in the directions of resorption and fusion of originally separate portions. In Teleosts the separate rudiments unite into a single mass which, in contrast with the course of events in Elasmobranchs, remain in connection with the gill epithelium. Growth is generally in a backward direction dorsal to the branchial arches, but the position varies in different species.

2. In Urodela the thymus arises in the form of compact outgrowths from the epithelium of the dorsal gill-pockets from 1 to 5.

In the Anura the organ arises exclusively from the second cleft.

In adult Amphibians the thymus lies behind and above the mandibular articulation. In the frog the gland is found behind the annulus tympanicus, covered by the depressor mandibulæ muscle. It is a small, longish, oval body, which may be 2 to 3 millimetres in length.

3. The thymus of reptiles has been specially investigated by de Meuron, Van Bemmelen, and Maurer. The organ

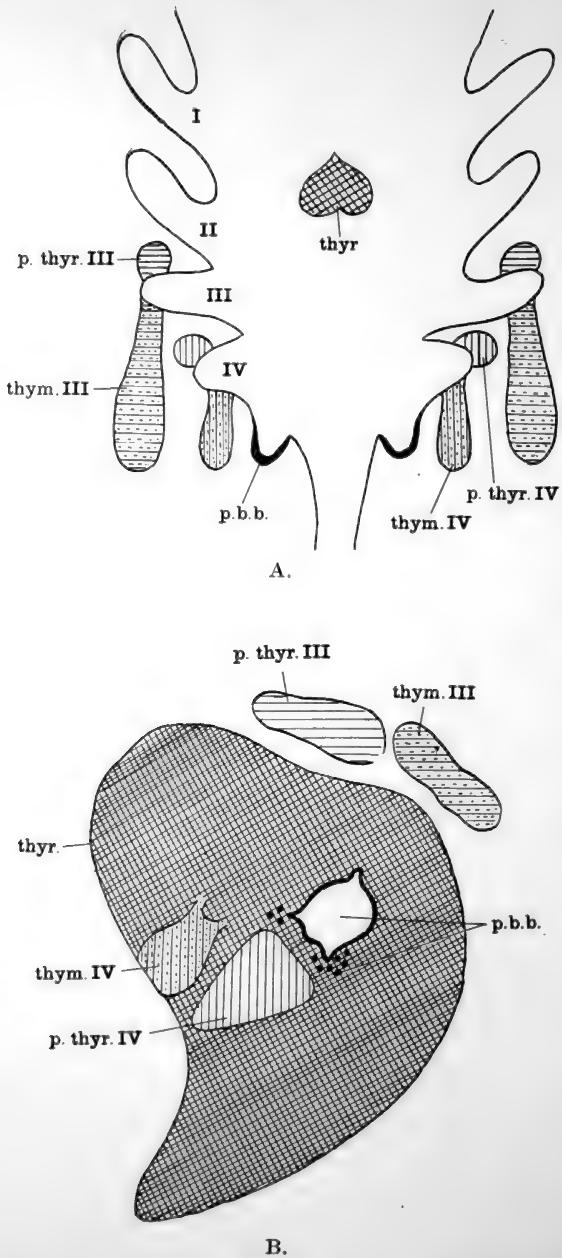

I
II
III
IV
thyr
p. thyr. III
thym. III
p.b.b.
thym. IV
p. thyr. IV
A.
p. thyr. III
thym. III
thyr.
p.b.b.
thym. IV
p. thyr. IV
B.

FIG. 90.

arises, as in the lower groups of vertebrates, from the dorsal gill-pockets, in the lizard from II. and III., in snakes from IV. and V.

4. In birds, thymus buds have been described from third, fourth, and fifth clefts.

5. The thymus of mammals apparently differs very materially in many respects from that of all lower animals, inasmuch as it is much more complex, and it is not the dorsal, but the ventral, pockets of the gill-clefts which furnish its rudiment. In most cases the third cleft is the most important, but sometimes the fourth, and occasionally, also, the second, plays a part. This portion of the origin of the gland is entodermal (see Fig. 90).

Recent work has confirmed the observations of Kastschenko as to the occurrence of an ectodermal component, derived from the "ductus præcervicalis," in the thymus of certain mammals. This conception must have a far-reaching effect upon our views as to the origin and nature of the mammalian

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Explanation of Fig. 90.

(*Diagrams* A. *and* B.).

A. illustrates the development of the branchial organs of mammals, B. shows their actual relations in the adult.

The different related rudiments of the same branchiomere are represented by a similar direction of shading lines ; so also the corresponding organs. Thus the rudiments from the third cleft are represented in A. by horizontal lines, as also the organs thus arising in B. The rudiments and organs from the fourth cleft are characterized by vertical lines. The post-branchial body is shown in thick outline, the thyroid by crossed lines.

The different kinds of tissue arising from one and the same branchiomere are indicated by differences in the shading. The parathyroid tissue is shown by lines, the thymus tissue by alternate continuous and interrupted lines. The post-branchial body is represented in the developed condition as a hollow space with several glandular nodules (shown in dark circles).

A. shows the four internal gill slits (I. to IV.), the epithelial origins of the parathyroids (*p. thyr.* III., *p. thyr.* IV.), the origin of the thymus (*thym.* III., *thym.* IV.), the rudiment of the thyroid (*thyr.*), and that of the post-branchial body (*p.b.b.*).

B. represents a schematic transverse section through the fully developed thyroid (at about the level of the junction of the upper and middle third of the thyroid lobe of a cat). The lettering corresponds to that in Diagram A. The structures which arise from the third cleft become the "external" parathryoid and thymus nodule (separated fragment of thymus III.) ; those which arise from the fourth cleft become the "internal" parathyroid and the thymus nodule (*p. thyr.* IV., and *thym.* IV.). The post-branchial body is surrounded by thyroid tissue.

(A. is after Groschuff in ruminants ; B. from Kohn in the cat.)

thymus. From a phylogenetic standpoint the ectodermal and the entodermal thymus representatives must be regarded as two distinct organs, which, through a parallelism in development, have acquired a similar structure.

There are three types of thymus in mammals:

1. A purely entodermal thymus. This is found in the human subject and in the rabbit.

2. A purely ectodermal thymus. This is found in the mole.

3. A mixed entodermal and ectodermal thymus. This condition is found in the pig and the guinea-pig.

While in crocodiles and birds the thymus is situated in the neck, in mammals it is for the most part situated in the thorax. But in some mammals there is a cervical portion as well as a thoracic portion, while, again, in some species, such as the guinea-pig, the structure is entirely cervical. How far the distinction between an entodermal and an ectodermal thymus corresponds to the cervical and thoracic representatives of the gland is not known. But it is stated that the cervical thymus of the guinea-pig is entirely entodermal, being derived from the third cleft, and corresponds to the human gland, which, however, is thoracic.

This acceptance of a dual origin of the mammalian thymus will necessitate a reinvestigation of the development of the organ throughout vertebrates. But it must be borne in mind that a definite statement as to whether a derivative of a gill-cleft is ectodermal or entodermal in origin is often a matter of extreme difficulty.

The human thymus is derived from the third visceral pouch, but it is not yet decided as to whether there is an accessory rudiment from the fourth pouch. The thymus is thus in its first origin bilateral. A pocket develops from the third cleft on each side, and extends itself as a thick-walled tubular prolongation along the carotid artery. The pocket persists as the "thymus vesicle" in the proximal section of each rudiment. From the lower end of the tube solid epithelial buds are given off, and from these lateral buds again come off, so that this part of the gland acquires a ramified lobular appearance like an acinous gland. The acini, however, are solid. The two rudiments are brought into close contact with one another in front of the trachea, and unite to form

a single-lobed body, which comes to lie in the anterior mediastinum in close relationship with the pericardium.

B. Structure of the Thymus

The thymus is made up of several lobules, which vary in size, and are separated from one another by connective-tissue septa, bearing bloodvessels and lymphatics.

Each lobule may be divided into a cortical and a medullary portion. The cortex is incompletely separated into "nodules" by connective-tissue trabeculæ, the arrangement bearing a strong resemblance to that of a lymphatic gland. The cortex is very vascular, and is similar in appearance to a lymphatic gland. Its structure also agrees with that of lymph glands and tonsils in exhibiting numerous signs of mitosis, but without definite germ centres. In addition to the lymph cells, there are also a number of peculiar granular cells.

The medulla, like that of a lymphatic gland, is more open in its texture than the cortex, and its reticulum is made up of large, transparent, branched cells, which are sometimes arranged in an epithelioid manner. The medulla does not contain so many leucocytes as the cortex, but is characterized by the presence of the peculiar concentrically striated bodies—the concentric corpuscles of Hassall (see Fig. 91). These vary very considerably in general appearance, and their precise origin and significance are still matters for discussion.

The above account is largely derived from that given by Schäfer. It seems possible that there are many points in connection with the thymus upon which current views may have to be changed. It has long been taught that the human thymus reaches its greatest development at about the second year, and then begins to degenerate. But it was shown in the year 1890 by Waldeyer that even in advanced age a considerable amount of thymus tissue persists, and probably maintains its function. Zoja had previously shown that the thymus frequently persists till the age of puberty. Recently Hammar has insisted that the organ continues to grow up to the period of puberty, and reaches its greatest development between the fourteenth and sixteenth years. From that time onwards it gradually loses in weight, but microscopical investigation shows that it still functions. A true atrophy of the

parenchyma, with elimination of function, comes on at about fifty to sixty years of age.

It seems, then, that we must regard the thymus as an organ regularly present, and probably in an active functional condition up to the age of puberty. The explanation offered by Hammar of the opposite conclusion reached by former anatomists is this: Wharton in the seventeenth century observed that a reduction in size of the thymus frequently occurred in exhausting or wasting diseases. This has been

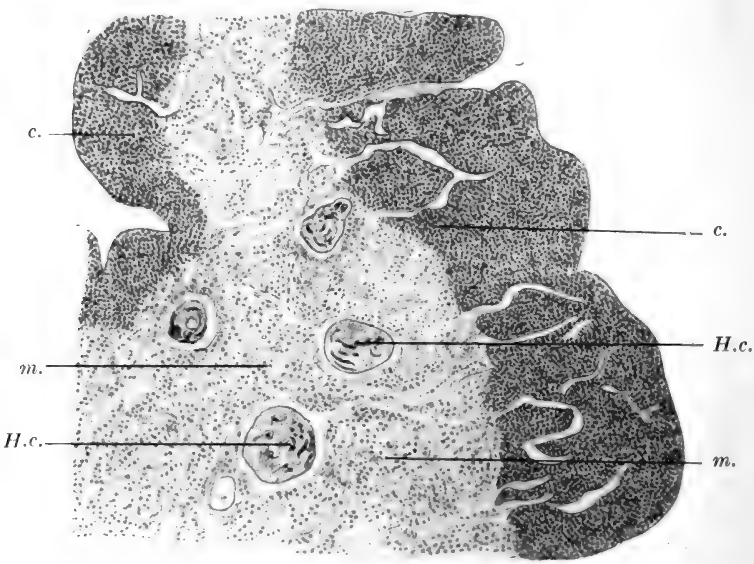


FIG. 91.—Portion of the thymus gland of a monkey, as seen under a low power of the microscope. (Drawn by Mrs. Thompson.)
c., cortex; *H.c.*, Hassall's concentric corpuscles; *m.*, medulla.

frequently noted, and so it has been customary to look upon the thymus as a kind of "barometer" to indicate the state of nutrition. But more often the mistake has been made of confusing this "accidental involution" with the age involution.

It seems somewhat doubtful whether we are to look upon the thymus in its fully developed condition as a lymphoid organ. According to Wiedersheim, "Jedenfalls stellt die thymus zu keiner zeit ein 'lymphoides Organ' dar." Hammar has brought forward evidence that, not only in its origin,

but throughout life, the thymus has the characters of an epithelial organ. But there are undoubtedly leucocytes present, and Hammar believes, as did the older observers, that these are of mesodermal origin, invading the gland secondarily, and there undergoing further proliferation.

Stöhr believes in the epithelial origin and nature of the small thymic cells. These arise *in situ* from the repeated multiplication of the reticular epithelium, and though morphologically they come to assume a structure indistinguishable from that of the true lymphocytes, they remain throughout true epithelial elements.

We have, then, four prevailing theories as to the nature of the thymus element: (1) That the original epithelial elements are entirely replaced by a leucocytal invasion from the mesoderm, and that the thymus in its fully developed condition is a lymphoid organ; (2) that the original epithelial elements give rise to lymphoid cells *in situ*, and that the thymus becomes a lymphoid organ; (3) that the thymus remains an epithelial organ, but that there are lymphoid elements which have invaded it; (4) that there are no true lymphoid elements, but that the small thymic cells, which appear to be of a lymphoid nature, are, in reality, epithelial. This last is the view of Pappenheimer.

If this last view be correct, we should expect to find some differences between these cells and lymphoid elements. The present writer has given some little attention to the structure of the thymus (apart from embryological considerations), and it would seem that many of the thymus cells are indistinguishable from the lymphoid cells. But the matter is still in a very doubtful state, and needs further investigation. The question is not only of morphological, but also of considerable physiological, importance. If the thymus cells are in truth epithelial throughout the life of the organ, we may with reason look for an internal secretion in the sense in which we defined it in an earlier chapter. On the other hand, if the cells be finally included among lymphoid elements, then we shall expect to find that the functions of the thymus are allied to, if not identical with, those of lymphatic glands.

Hammar's most recent view is that the thymus is an epithelial organ with a leucocytal infiltration. Hassall's corpuscles

represent a functional differentiation of the epithelium. Under the influence of certain common disturbances, the thymus may undergo an "accidental involution" of a more or less transitory nature. Puberty normally brings on an "age involution," which is brought about by diminution of the leucocytal part of the organ, then by increased degenerative processes, by which the function of the organ and gradual destruction of the parenchyma are brought about.[1]

Pigache and Worms report an "accidental involution" after thyroidectomy in dogs and rabbits; while Utterström finds that feeding rabbits with thyroid substance has two distinct and opposing actions on the thymus, the one a depressor action due to the condition of reduced nutrition, the other a direct thymus excitation. This last action explains the enlargement of the thymus found in cases of exopthalmic goitre. Hoskins notes that this hypertrophy of the thymus after thyroid feeding affects only the cortex.

FIG. 92.—Hassall's concentric corpuscle from the thymus of a cat. This body shows a typical concentric arrangement. (Drawn by Mrs. Thompson.)

It has been proved that leucocytes are already present in the body before the lymphoid transformation of the gland, so that the thymus cannot be the original source of the leucocytes, as suggested by Beard.

In regard to the Hassall concentric corpuscles modern investigation appears to show that these structures are not to be looked upon simply as remains of the original epithelium which have not become transformed into lymphocytes. Hammar has shown that the concentric corpuscles are derived from hypertrophic reticular cells. The formation of these structures begins early in fœtal life, and continues long into the period of post-natal evolution of the organ. Wallisch has pointed out that the total volume of the Hassall bodies

[1] The bursa fabricii of birds is an organ which in some respects may be regarded as analogous to the thymus. Thus it undergoes leucocytal invasion and a degeneration at about the age of puberty.

in young children exceeds that of the whole thymus in a three months' embryo.

It will not be possible to give a full account of the various thymus elements. One other thymic structure must, nevertheless, be briefly referred to. In 1888 Sigmund Mayer described certain peculiar elements in the frog's thymus. These he regarded as rudimentary voluntary muscle fibres. Similar structures were observed in Teleosts by Schaffer, who described them as sarcolytes in various stages of disintegration. Similar structures which have been discovered in birds and reptiles are considered to be of a muscular origin and nature. Hammar, however, regards them as specially differentiated hypertrophic reticular cells, and therefore as closely related to the concentric corpuscles. Pappenheimer has recently found these myoid cells in the human embryonic thymus, and holds the same view as Hammar as to their nature and origin.

C. Extirpation of the Thymus

Abelous and Billard reported that the removal of both thymus glands in the frog always resulted fatally within three to fourteen days. Ver Eecke, however, pointed out that death did not occur if precautions against infection were taken by regularly renewing the water in the frog-tanks. The latter investigator was of opinion that removal of the thymus lowers the resistance of the frog to septic influences, and that this accounts for the fatality in the experiments of Abelous and Billard.

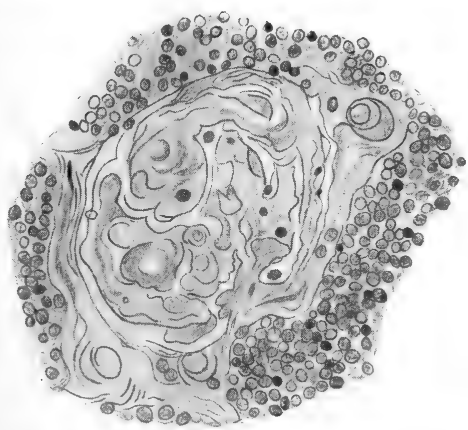


FIG. 93.—Hassall's concentric corpuscle from the human thymus gland. The concentric arrangement is not so regular or so marked as in the cat. (Drawn by Mrs. Thompson.)

The present writer came to the conclusion that in the case

of frogs extirpation of both thymus glands does not necessarily end fatally. Some of the animals experimented upon survived as long as thirty-six days, and have either been killed at the end of this time or have died of some cause independent of the operation.

The earliest experiments upon mammals appear to be those of Friedleben. This observer operated upon twenty dogs and three goats; none of his animals died as the result of the thymus extirpation.

Tarulli and Lo Monaco found that in dogs the thymus is not an indispensable organ. Only in very young animals had extirpation any results; there were in these cases disturbances of nutrition, diminution of muscular power, diminution in the number of the red blood-corpuscles, and of hæmoglobin, etc. These disturbances were only of short duration, and disappeared when the dogs grew older.

The present writer could not ascertain that the removal of the thymus in guinea-pigs affects the animal in any way whatever. Litters of guinea-pigs of ages varying from ten days to a month were procured, and while some of the litter were submitted to operation, others were kept as controls. The young guinea-pigs appeared perfectly well an hour after the operation, and no symptoms of any kind supervened. They grew at the same rate as the controls, and no signs of changes in the blood were detected.

Within the last few years the thymus has received a great deal of attention, and a large amount of anatomical and physiological work has been carried out. The conception of the thymus as being not altogether a lymphoid organ seems to be gaining ground. A nutritive rôle has been suggested for the gland on account of the richness of the tissue in purin bodies. On the whole, the verdict seems to be that the organ is not essential to life, even in quite young animals.

In young dogs it is stated that changes can be detected some months after extirpation of the thymus. The nutritive processes became defective, and none of the animals lived more than a year. On post-mortem examination, enormous dilatation of the heart was usually discovered. It is suggested that the thymus has an action antagonistic to that of the adrenal, so that, when the former is removed, there is a predominance of adrenal activity, and consequently hypertonus

of bloodvessels and dilatation of the heart. Grafting additional thymus glands into young dogs caused serious disturbances to health (Hart and Nordmann).

Klose, and Klose and Vogt, performed a series of extirpation experiments upon dogs between ten days and four weeks old. These authors divide the post-operative period into three stages: (1) A latent period, lasting from two to four weeks; (2) an adipose stage, which lasts two or three months; and (3) a cachectic stage, or the stage of "cachexia thymopriva" and "idiotia thymopriva." This period extends to three to fourteen months. Death occurs with "coma thymicum," which often lasts a long time. The skeleton remains hypoplastic and dwarf-like, and the bones become atrophic. There is a deficiency of undissolved calcium. Bodily movements are feeble, and there are disturbances in the nervous system.

Interference with the growth, especially of the skeleton, is also described by several observers.

Changes in the pituitary and in the spleen after thymectomy have been recorded. Perrier states that in the pituitary there is an increase of the chromophilic cells. In the spleen there is an increase of the reticulum and a hypertrophy of the lymphoid tissue.

The thymus does not appear to have anything to do with the formation of red blood-corpuscles, nor with the growth of epithelial organs.

Soli states that extirpation of the thymus in adult hens causes them to lay eggs without shells. This is the only evidence which has been put forward up to the present time that the thymus has any function after the period of involution of the organ.

D. A Probable Relation between the Thymus and the Reproductive Organs

Calzolari in 1898 suggested a relationship between the thymus and the reproductive organs, and performed a series of experiments upon rabbits, with the object of putting the matter to the test. He found that in castrated male rabbits the volume and the absolute weight of the thymus were greater than in normal animals. He concludes that the

thymus atrophies move slowly in animals from whom the testes have been removed.

Henderson obtained similar results in rabbits, guinea-pigs, and cattle. He states, further, that in bulls and unspayed heifers the normal atrophy of the thymus which begins after the period of puberty is greatly accelerated when the bulls have been used for breeding, and when the heifers have been pregnant for several months. The retarded atrophy is due, according to Goodall, to a persistent growth of the lymphoid tissue, a delay of the fatty invasion, and a delay in the process of disintegration of the epithelium composing the Hassall's corpuscles.

According to Marrassini and Gellin, castration gives rise to an enlargement of the thymus. Squadrini believes that castration interferes with the normal involution of the gland. From these observations it would appear that the normal involution of the thymus is due to the development of the reproductive organs, though this cannot be the only cause. The experiments, further, tempt one to the hypothesis that the thymus furnishes an internal secretion of some kind which ministers to the needs of the economy before the reproductive organs are fully developed. Normally this internal secretion is provided by the testes (or ovary) after puberty, but if castration is performed, the thymus maintains its original structure and functions. This internal secretion must, of course, be of a different nature from that which determines the development of the secondary sexual characters, as these do not become manifest in castrated animals.

It must be added that recent careful experiments by Parke cast considerable doubt upon the intimate relation between testis and thymus.

E. Physiological Effects of Extracts of Thymus

Svehla found that the thymus of the ox during embryonic life yields to extracts a substance which lowers the blood-pressure. This he considers as a manifestation of an internal secretion. From what has been said in an earlier chapter, it is clear that this depressor substance is simply that unknown material which is common to all animal tissues and organs. It is not specific for the thymus.

F. Pathology of the Thymus

Perhaps the chief medical interest attaching to the thymus arises from certain remarkable cases of thymic death ("mors thymica"). In cases of thymic enlargement the essential symptom is a respiratory disturbance resulting from the diminution of space in the superior thoracic strait. This disturbance may vary from a mild stridor to a fatal dyspnœa. Sometimes the dyspnœa is of an asthmatic character ("thymic asthma").

"Mors thymica" is a term applied to those cases in which death occurs suddenly, without a definite history of previous respiratory difficulty. This may happen even when there are no other symptoms of the status lymphaticus, but very frequently this condition is present, and the thymus enlargement is associated with adenoids, and with enlarged tonsils and lymphatic glands.

The cause of death in these cases has been the subject of much discussion. It is probable that in the majority of instances the case is one of suffocation from tracheal stenosis and secondary laryngeal spasm. It seems certain that many cases of so-called "mors thymica" are not of thymic origin. At any rate, a detailed discussion of this subject is not likely to shed light on the function of the organ.

Some cases of Addison's disease appear to be combined with the status lymphaticus.

CHAPTER XV

THE FUNCTION OF THE PITUITARY BODY

A. Comparative Anatomy of the Pituitary Body

1. *The Mammalian Pituitary Body*

RATHKE was the first to point out the double origin of the pituitary body, from the brain and from an invagination of the mucous membrane of the alimentary tract. Other observers of this period looked upon the body as part of the brain. Luschka called the body a "nerve gland," consisting of two parts, separated by pia mater; while Ecker includes the structure of both portions under the name "Blutgefässdrüsen."

Burdach regarded the nervous portion as the "filum terminale anterius" of the cerebro-spinal canal; and Virchow and others noticed in the anterior portion colloid vesicles like those of the thyroid.

The anterior lobe is admittedly glandular in its nature, but the structure of the posterior lobe has been variously described. Earlier writers looked upon it as a mass of connective-tissue cells and fibres, which, during the course of development, have destroyed all trace of the original nerve tissue. Berkley described nerve cells and glia cells in the posterior lobe. Kölliker speaks very doubtfully about the matter, even about the results of investigation by the silver chromate matter.

Osborne and Swale Vincent could detect only very few undoubtedly nerve cells in the infundibular portion. These observers also confirmed and utilized experimentally the fact that the posterior lobe has an epithelial investment.

The pituitary body consists of three portions: (1) The anterior lobe; (2) the intermediate portion; and (3) the posterior lobe, or nervous portion.

There are three types of mammalian pituitary body. In the first, of which the organ of the cat furnishes an example, the posterior lobe is hollow, and its cavity is in free communication with the third ventricle of the brain, and the epithelium of the anterior lobe almost completely surrounds the posterior lobe. In the second type (as, for example, in the dog) the body of the posterior lobe is solid, but the neck is hollow, and communicates with the third ventricle, and the posterior lobe is almost completely surrounded with epithelium, as in the first type. In the third type—*e.g.*, man, monkey, ox, pig, and rabbit—the body and neck of the posterior lobe are solid, although traces of a cavity are occasionally found in the neck. In this last type the epithelium of the anterior lobe does not spread so far round the posterior lobe, but is gathered around the neck and spreads over and into the adjacent surface of the brain (Herring). (Fig. 94.)

The epithelial portion is again divided into two parts: (1) An anterior lobe proper, consisting of solid columns of cells, between which run wide bloodvessels; and (2) an intermediate portion, which lies between the anterior lobe and the nervous portion, forming a close investment to the latter. (Figs. 94 and 95.)

The anterior lobe presents all the appearances of a true internally secreting gland. Its structure is clearly that of a gland—an "epithelial body," in Kohn's phraseology. It is made up of a branching, compact network of epithelial threads and columns. In the spaces of the epithelial network run wide, thin-walled bloodvessels, so that in many cases the epithelial cells are placed directly on the delicate vessel wall. This arrangement is most admirably adapted for the purposes of internal secretion. The general scheme of structure is the same as in the adrenal cortex, the islets of Langerhans, of the pancreas, the thyroid, and the thymus (in its epithelial stage). (See Fig. 95.)

The general nature of the cells found in the glandular pituitary may be thus stated:

1. Chromophile $\begin{cases} (\alpha) \text{ Acidophile.} \\ (\beta) \text{ Basophile.} \end{cases}$

2. Chromophobe. (See Fig. 95.)

Besides the colloid, it is probable that there are other secretory products.

In no other endocrine gland are the granular products of secretion so well seen as in the anterior lobe of the pituitary body. Secretory granules are also seen in the vessels belonging to the gland.

Leyton, as a result of, the examination of a large number of human pituitaries, came to the conclusion that colloid material may be found in the bloodvessels, both in the anterior lobe and also in the so-called pars intermedia. Colloid material was not seen in the pars nervosa.

In children and in the fœtus the distinction between the different varieties of cells in the anterior lobe is not marked, and colloid material is small in amount.

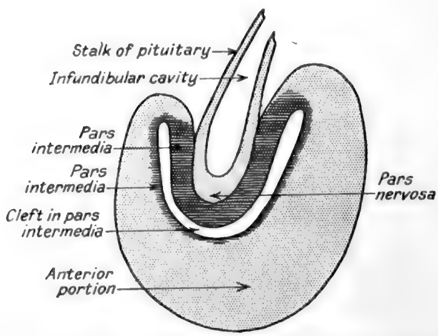


FIG. 94.—Diagram showing relations of principal parts of pituitary body.

The size and weight of the gland and the amount of colloid material are subject to very great variation.

Cushing and Goetsch find colloid masses in the posterior lobe of the pituitary, and agree with Herring that the colloid masses in this lobe are secretory products of the epithelial covering of the pars intermedia. They find in the cerebrospinal fluid a substance which gives the same reactions as the pars nervosa itself.

The intermediate portion consists of finely granular cells

arranged in layers of varying thickness closely applied to the body and neck of the posterior lobe and to the under-surface of adjacent parts of the brain. The part of it which is separated from the anterior lobe by the cleft is almost

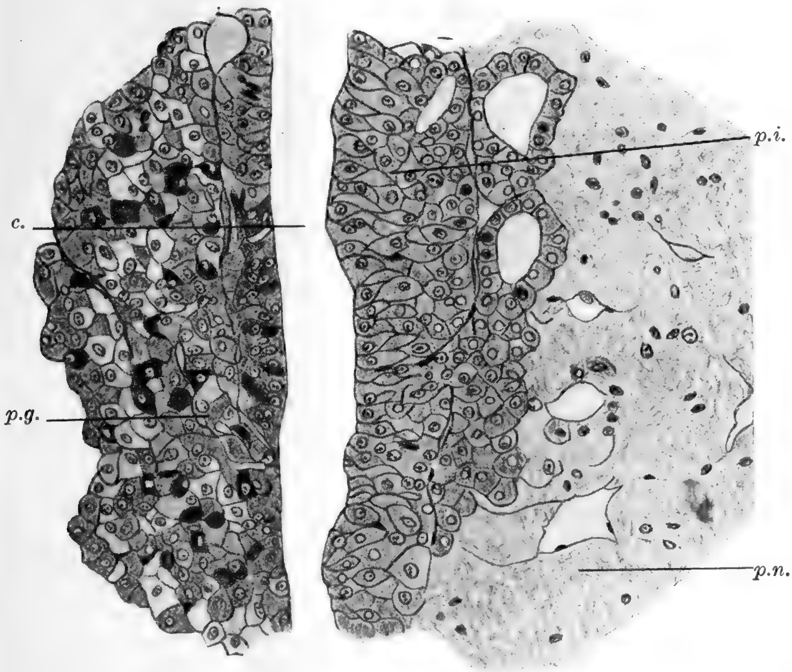


Fig. 95.—Section through a portion of the pituitary body of the dog, showing the glandular and nervous portions and the pars intermedia. (Drawn by Mrs. Thompson.)

c., cleft in glandular portion (between glandular portion proper and the intermediate portion); *p.g.*, glandular portion; *p.i.*, intermediate portion; *p.n.*, nervous portion.

In the glandular portion are seen three kinds of cells.

devoid of bloodvessels. Colloid material occurs between the cells of the pars intermedia. (Fig. 95.)

The nervous portion is made up of neuroglia cells and fibres, and is invaded by the epithelial cells of the pars intermedia. A substance resembling the colloid of the thyroid gland occurs in the nervous portion. The glia cells are longish

or cylindrical, with one, two, or more nuclei, and a granular, at times pigmented, cell protoplasm. From the protoplasm stretches a long, thin homogeneous fibre, which is sharply contoured, like an elastic fibre. These cells are young forms of ependyma cells—the "radial cells" of Retzius. In addition, there are "protoplasmic cells" which are multipolar, and send out fine glia fibres. There are also "spindle cells," "giant glia cells," "keratin cells," etc. All these build up a primitive neuroglia.

One of the most interesting features of the posterior lobe is the pigment, which has been known for a long time. According to Kohn, the pigment is contained within the threads of the neuroglia, and distends them here and there. When unstained, the substance is of a greenish-yellow tinge, and consists of closely packed, irregular clumps. The amount of the pigment is found to become notably increased in age and disease. For this reason it is supposed to represent some kind of breakdown product. It has been suggested that the pigment bears some relation to the functions of the organ, and especially to the secretion of the anterior lobe.

Clunet and Jonnesco have also given an account of the pigment in the neurohypophysis. According to these authors, the substance does not give the iron reaction. It is insoluble in alcohol, xylol, benzol, cedar oil, chloroform, and ether. It is stained red with osmic acid, red also with Sudan and Scharlach red, while it is blackened with iron hæmatoxylin.

Haberfeld finds in the human subject at all ages a "pharyngeal pituitary"—a solid string of cells about 5 millimetres long, which runs from below upwards and backwards immediately behind the vomer. It contains cells like those in the pituitary itself, but here the chromophobe elements predominate, and the basophiles may be absent. Histologically it resembles the pars intermedia. It is the origin of most of see p. 37 the pituitary tumours. This structure is probably the remains of the original pituitary duct.

Haberfeld describes a cystic structure in intrauterine life, which is made up of glia cells and fibres, and possessing lumina, surrounded by ependyma cells. This body is frequently, he alleges, the starting-point of gliosarcomata.

Staderini gives an account of the "eminentia saccularis" (an elevation on the base of the brain immediately behind the

stalk of the pituitary). He considers that the structure is not homologous with the "succus vasculosus" of fishes, as Retzius thought.

A very rare abnormality which has been described in connection with the sphenoid bone is a persistent, perforating foramen in the basisphenoid—the canalis craniopharyngeus. This is regarded as the place of exit of the original duct of the anterior lobe of the pituitary body.

Haberfeld finds the canal wanting in all acromegalic skulls in the Vienna Pathological Institute. He reports that it is very variable in individuals of the same species of animals. He calls attention to the fact that the pharyngeal pituitary is constant in man, while it is frequently absent in the lower animals. This is not what would be expected if the structure really represents the remains of the original duct of the pituitary.

2. *The Pituitary Body of Birds and Lower Vertebrates*

In birds the epithelial cleft appears to be absent. The cells of the anterior lobe are for the most part small and finely granular.

The posterior lobe is small and hollow, and much convoluted. Colloid bodies are sometimes present. The cells of the pars intermedia come into close contact with the nervous portion of the posterior lobe, but are gathered together for the most part in the neighbourhood of its neck and on the thin lamina of nervous tissue forming the floor of the third ventricle.

In Teleostean fishes the posterior lobe has a complex vascular structure of a glandular nature, which was called the "saccus vasculosus" by Göttsche.

The Teleostean pituitary is composed of three kinds of tissue, two of which are epithelial and the third nervous, the latter being comparatively small in amount. The anterior lobe of mammals is represented by a wedge-shaped mass of large and deeply staining cells. These cells vary in situation and extent in different species. The pars intermedia consists of small, round, feebly staining cells, which surround and invade the nervous tissue. The pars intermedia in the cod is divided into two main portions, which are continuous

with, and separated from one another by, the true anterior lobe (Herring).

The nervous part of the cod's pituitary is small, and appears to be composed of neuroglia and ependyma cells, without any true nerve cells. It is continuous with the brain in front by the lamina post-optica, or anterior lamina, and at the sides by lateral laminæ. The nervous substance is more freely invaded by cells of the pars intermedia than is the nervous substance of the mammalian body.

In Elasmobranchs (*Raja batis*) the pituitary is a long, club-shaped body which lies for the most part behind the small lobi inferiores. Its structure is very different from that of mammals, birds, and Teleosts. There are no cells having the deeply staining characteristic of those of the anterior lobe of other vertebrates, and there are no cells exactly like those of the pars intermedia. There is no differentiation into anterior and posterior lobes, and the only trace of a posterior lobe is a thin lamina of nervous tissue which bounds the infundibular cavity. The saccus vasculosus is well developed. The Elasmobranch pituitary appears to be quite different from that of other vertebrates.

B. Development of the Pituitary Body

The earlier observers believed that the whole of the pituitary body is derived from the brain. Rathke, however, described the invagination of mucous membrane, since called "Rathke's pouch," and put forward the view that from this pouch is derived the epithelial portion of the pituitary (which he further stated has been derived from the entoderm of the fore-gut).

Dursy described the origin of the epithelial part from the fore-gut, and of the vascular stroma from the notochord. W. Müller showed that the anterior lobe arises from Rathke's pouch, but believed this to be entodermal. It is now usually considered that the pouch is of ectodermic origin.

The posterior lobe was originally conceived as the anterior extremity of the brain, but more recent researches have shown that it is an outgrowth of the thalamencephalon.

Mihalkovics has given a complete account of the early development of the pituitary body in the rabbit and the chick. According to this author, the anterior lobe is developed from

Rathke's pouch, and is ectodermal. The beginning of the pouch is in front of the oral plate. When this ruptures, its upper stump, containing in its upper part the head of the notochord, bends forward and narrows the mouth of the epithelial pouch, leading to the formation of a definite sac—the hypophysial sac. The wall of the sac presses upon the base of the anterior brain vesicle, giving rise at its upper extremity to a fold in the wall of the brain, which becomes the primitive infundibulum. The primitive infundibular process comprises the surrounding tissue of the tuber cinereum as well as the origin of the infundibulum, and the true infundibulum is formed at a later stage by its own growth from a portion of the primitive infundibular process. The head of the notochord, beyond presenting a barrier to the backward growth of the sac, takes no part in the formation of the pituitary body.

Mihalkovics' work has been confirmed in the main by numerous authors. Kupffer described an additional origin of part of the anterior lobe of the pituitary from the entoderm of the fore-gut, and this view has received support. Herring, however, believes that the epithelial portion of the pituitary is entirely ectodermic. The account of the last-named author is briefly as follows:—

Development of the pituitary body begins very early in embryonic life. In mammals the epithelial portion is derived entirely from the ectodermic wall of "Rathke's pouch." Its origin is single and mesial. The epithelium is early distinguishable into two parts. One of these—the intermediate part—is closely adherent to the wall of the cerebral vesicle; the cells are clear, and tend to form colloid. The other portion of the buccal epithelium gives rise to the anterior lobe proper. Its cells are granular, and form solid columns separated by blood-channels.

The infundibulum is an invagination of part of the wall of the thalamencephalon, which is adherent to the anterior and upper wall of Rathke's pouch. It therefore possesses an epithelial covering derived from the latter. The infundibular process grows backwards, and, in the cat, retains its central cavity. It is lined by ependyma cells, which, during development, become elongated, so that ependyma fibres run obliquely in its neck. The posterior lobe of the pituitary is, from the

first, a composite structure of epithelium of the pars intermedia and of neuroglia and ependyma, and the relations between the two tissues become more and more intimate.

The early stages of development of the Elasmobranch pituitary resemble those in the mammal, except that there is no invagination of the wall of the cerebral vesicle in Elasmobranchs to form an infundibular lobe. The body is derived entirely from the buccal epithelium of Rathke's pouch.

The relation of the pituitary to the brain ventricles is similar to that in higher vertebrates, but this is accounted for by the development of a paired saccus vasculosus, each of which pours its secretion into a common infundibular canal. The wall of this is lined with epithelium similar to that lining the saccus vasculosus. Its nervous structure is lost, being replaced by connective tissue and numerous thin-walled bloodvessels. There is no invasion of the wall of the canal by epithelial cells, and no hyaline bodies are formed.

The pituitary body of the Elasmobranch is a gland, the secretion of which is poured directly into the bloodvessels. There is no evidence of any direct secretion by the pituitary into the brain ventricles.

C. **Older Views as to the Functions of the Pituitary Body**

The oldest theory concerning the pituitary body is transmitted by, and survives in, the name the organ bears. The secretion of the mucous membrane of the nose (pituita) was supposed to be derived from the "glandula pituitaria." This was the view of Galen, held also by Vesalius. At the period of Vieussens and Sylvius, the body was supposed to have to do with the formation of the cerebro-spinal fluid.[1]

Cushing calls attention to a remarkable paper by Lower (*Dissertatio de Origine Catarrhi*, 1672), who was the first experimentally to disprove the Galenic doctrine. "For whatever serum is separated into the ventricles of the brain and tissues

[1] It is interesting, as pointed out by Cushing, to note that a substance from the gland may under certain conditions enter the nose, and that, according to modern conceptions, the pituitary body does add something to the cerebro-spinal fluid.

out of them through the Infundibulum to the Glandula pituitaria distils not upon the palate but is poured again into the blood and mixed with it."

Majendie regarded the pituitary as a kind of lymphatic gland, which collects the cerebral lymph and passes it into the circulation. "Its pars anterior does discharge its elaborated products into the circulation, and the pars nervosa apparently contains certain inter-neurogliar spaces resembling lymph channels."

For a long period, the pituitary body was looked upon as a "vestigial relic," and of no importance in the animal economy.

The association of Addison's disease with adrenal lesions was the starting point of adrenal physiology, and the connection between myxœdema and thyroid mischief was the beginning of our knowledge of the functions of the thyroid. In the same way, the appearance of Marie's publications (1888–1889) on acromegaly and pituitary tumours, was the chief impetus towards all the modern investigation into the structure and functions of the hypophysis cerebri.

Of supreme importance in the history of our knowledge of the pituitary, as indeed of all the ductless glands, was the discovery by Oliver and Schäfer (1894) of the physiological activity of adrenal extracts. This led directly to the observation by the same authors of the power in raising blood-pressure of extracts made from the pituitary body, and has instigated a vast amount of work depending on the investigation of the action of various tissue extracts upon the body generally and on the different systems.

D. Physiological Action of Extracts of the Pituitary Body

1. *Effects on the Heart and Bloodvessels*

Oliver and Schäfer discovered that aqueous or saline extracts of the pituitary body produce, when injected into the bloodvessels, a rise of blood-pressure, which is comparable to that produced by extracts of the adrenals. The rise is produced by an action on the peripheral arterioles, as is that brought about by adrenal extracts. The action of pituitary extracts, however, is more prolonged than that of adrenal extracts.

There was no marked effect upon the rate of the heart-beat. (See Figs. 96, 97.)

Howell made a considerable step in advance. He divided the gland into its two chief portions—the anterior and posterior lobes—and determined that, while an extract of the former is devoid of physiological activity when injected into a vein, that of the latter produces the effects upon the blood-pressure. Howell further found the rise of blood-pressure to be accompanied by a slowing of the action of the heart, and that both the raised blood-pressure and slow cardiac rhythm might be maintained for a considerable time; and that if a second dose be administered intravenously within a certain time—which varies from half an hour to an hour or more—after the first dose, these effects are not repeated—in other words, a certain immunity is established, which only slowly passes off.

Cyon has noticed, as did Howell, that the rise of blood-pressure is accompanied by slowing of the pulse. Both these effects he attributes to stimulation of the pituitary body by the extract which has been injected. He states that stimulation of the hypophysis in the body, either electrically or mechanically, will produce similar results through the vagi, and that after extirpation of the organ the effects can no longer be produced by injections.

There is slowing of the isolated mammalian heart, if extract of the "posterior lobe" be perfused through it.

Schäfer and Vincent, working with cats, found that pituitary extract, on administration of a second or third dose, always produces a fall, and not a rise, of pressure (see Fig. 97). The depressor substance was subsequently shown, by the present writer and collaborators, to be common to extracts of all organs and tissues.

Osborne and Vincent, working with dogs, found, with Howell, a preliminary fall before the rise, but, in most cases, a rise as well as a fall on a subsequent injection. This is what I have observed in a recent series of experiments.[1]

The main facts have been found to hold good as well for extracts made from the human pituitary.

According to Schäfer and Vincent, the cardiac slowing is

[1] In one experiment, even the first administration of pituitary extract produced no rise, and this result seems to have been due to the previous administration of adrenin.

not constant, and, when present, it is not abolished by section of the vagi or the action of atropine. It is, therefore, of peripheral origin, and is not due to the same cause as the inhibition which often accompanies the action of adrenin, and is brought about by an action on the cardio-inhibitory mechanism in the bulb.

This action of pituitary extracts upon the heart and blood-

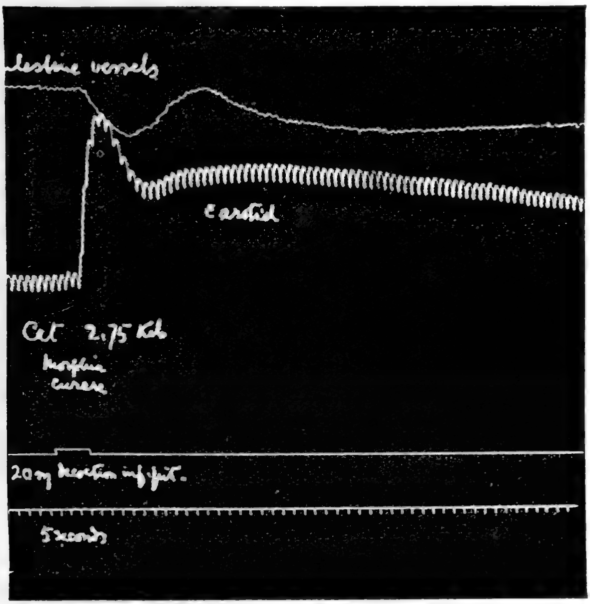


FIG. 96.—Effect upon the arterial pressure and intestinal volume of intravenous injection of decoction of infundibular body. Cat under morphine and curare. The time of marking indicates five seconds.

vessels is a special case of their action upon most of the involuntary muscles. The rise of blood-pressure already referred to is due to constriction of many of the bloodvessels of the body, combined with augmentation of the heart-beat.[1]

With large doses, the depressor effect may be so marked as to mask the usual subsequent rise.

[1] Paton and Watson state that in the duck there is dilation of vessels and not constriction.

According to Howell, the responses become less and less pronounced with each repeated injection. There is great variation in the effects produced not only between different species of animal, but even between different individuals of the same species.

It has been doubted whether the depressor action, seen with injections subsequent to the first, is wholly due to a different principle, though the evidence before us seems to the present

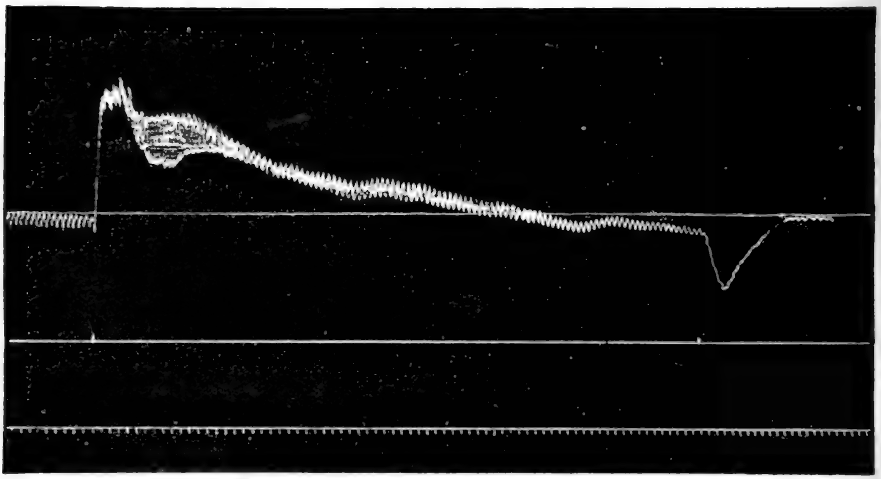


FIG. 97.—Effect upon the arterial pressure of intravenous injection of decoction of infundibular body. Cat. Morphine and curare.

writer to be strongly in favour of such a view. Hoskins and McPeek discuss the question, whether the pressor effect of pituitary extract is due to adrenal stimulation, and come to a negative conclusion. Experiments upon the isolated heart of the frog and of mammals show that the slowing of the heart-beat is due to a direct action upon the musculature of the heart. Einis finds that the first effect of pituitary extract upon the heart is a diminution of the frequency, this is followed by an increase.

2. *Effects on the Vasomotor Reflexes*

The facts that adrenin diminishes the excitability of the

vagus,[1] and that fluid from the thyroid appears to increase the excitability both of the vagus and the depressor, led to an investigation of the action of these and other tissue extracts upon the vasomotor reflexes.

The extract of the pituitary body, sold under different names by different firms, appears to convert a depressor reflex into a pressor, or very considerably to exaggerate the pressor effect. The latter effect is, in some cases, much more marked after previous administration of adrenin. This action of pituitary extract occurs only on a first injection.

Brisk kneading of the intestines evokes normally a very distinct vasomotor response, which is frequently accompanied by a slowing of the heart-beat. The effect upon the heart is very noticeable after the administration of pituitary extract, and the beat is frequently of a grouped character.

3. *Effects on the Respiration*

Mummery and Legge have noted a diminution of the amplitude of respiration, as a result of pituitary injection. Pantow states that breathing stops for some time after the injection, then begins again, then once more stops ; the primary stoppage appears to be due to peripheral vagus stimulation.

4. *Effects on involuntary Muscles other than those of the Vascular System*

(*a*) *The Uterus.*—It was first recorded by Dale that infundibular extract excites uterine contractions. The observation was confirmed by several investigators. The uterus is extremely sensitive to the action of the extract, whether in the body or treated as an isolated organ. Kehrer first used the uterus in the latter way, and noted the action of pituitary extract upon it. Engeland and Kutscher affirm that they have succeeded in separating, by a method of fractional precipitation, from an extract of the whole pituitary body a basic fraction possessing the characteristic action on the uterus, but not that on the blood-pressure. According to Dale and Laidlaw, the isolated horn of the uterus of the non-pregnant cat gives fairly good results, responding with but

[1] This is not always the case ; the precise conditions under which this occurs require careful investigation.

little diminished contraction to a second dose, after the first has been carefully washed away. It is subject, however, to inconvenient spontaneous slow variations of its average tonus, and is apt to acquire a disconcerting rhythm. The uterine horn of the young virgin guinea-pig is greatly superior in these respects, its natural tendency, when left undisturbed in the Ringer's solution, being to acquire a condition of complete relaxation, broken only by a small rhythm. It is very sensitive to the extract, which can therefore be given in very small doses, and the tissue normally relaxes with promptitude to its original level of minimal tonus on washing out and changing the solution. This method is found to detect differences of activity which escape recognition by the blood-pressure test, and is employed by Dale and Laidlaw for standardizing pituitary extracts.

(*b*) *The Bladder.*—The action of pituitary extract on the bladder was first noted by Bell and Hick. In dogs and cats, pituitrin stimulates to a considerable extent the musculature of the bladder, and increases the excitability of the pelvic nerve.

(*c*) *The Intestine.*—Bell observed the power of pituitary extract to restore peristalsis to the paralytically distended bowel, a capability which, according to Dale and Laidlaw, is not represented by any definite action on the bowel of the normal animal. But Beyer and Peter, working with the surviving small intestine of rabbits, find that, after a preliminary diminution in rhythm and tone, both these are very strikingly increased. The rhythmical movements are often increased tenfold. The first phase is considered by the authors to be due to stimulation of the sympathetic fibres which inhibit the muscle. The second phase, on the other hand, is due to stimulation of Auerbach's plexus and the post-ganglionic fibres. With very powerful doses, this second effect is very slightly manifested or may be absent altogether, so that an immediate and lasting inhibition may be the only result.

It is usually supposed that the most distinctive difference between the action of adrenin and that of pituitrin is that the former relaxes the unstriped intestinal muscle, while the latter uniformly contracts these fibres. But it has been shown by Shamoff that certain posterior lobe preparations are capable of producing relaxation of the isolated intestinal loop and of

inhibitingitsrhythmical contractions, resembling in this respect the extracts of the chromaphil tissues.

Just as Schäfer and Vincent found two separate substances acting on the blood-pressure—a pressor and a depressor—so Beyer and Peter distinguish two separate substances having respectively the two actions on the intestine just described, the sympathetic inhibitory substance being insoluble in alcohol, the autonomic augmentor substance soluble.

These effects on the intestine can be repeated at frequent intervals, while the effect on the bladder rapidly becomes less in successive trials.

It is doubtful how far these effects are truly specific for extracts of pituitary.

(*d*) *The Stomach.*—The effects of pituitary extract on the stomach appear to resemble very closely those upon the intestine just described. There is at first some inhibition, which is followed by a powerful and persistent augmentation. The rhythmical movements are very markedly exaggerated. These actions were first noted by Houssay in the frog, and then in other animals and man.

Clinical observations have been made in the same direction.

(*e*) *The Pupil.*—It was discovered by Cramer that pituitary extract dilates the pupil of the enucleated frog's eye. Franchini noted also that the serum of animals which have received intravenous injections possesses slight mydriatic properties.

There is thus a close resemblance between the reactions, due to administration of pituitary (posterior lobe, infundibular) extracts and those so familiarly called forth by means of adrenin. The chief differences consist in the preliminary fall (in some animals) and prolonged rise due to pituitary, and the fact that this drug causes slowing of the pulse after atropine or section of the vagi, in the constriction of the coronary and dilatation of the renal vessels, adrenin having an opposite effect.

5. *Effects on the Secretion of Certain Glands*

(*a*) *The Mammary Gland.*—Ott and Scott discovered that injection of pituitary extract into goats causes a marked increase in the flow of milk. Schäfer and Mackenzie found that ex-

tracts of pituitary body, corpus luteum, pineal body, involuting uterus, and lactating mammary gland all manifest a galactagogue action, but the pituitary body produces the most marked results.

Gavin found that the daily yield of milk in cows is not increased by the administration of corpus luteum and pituitary extract. Schäfer also reports that injection of pituitary extract into a muscle of a lactating woman caused only a temporary increase in the flow of milk.

It has been suggested that the hypertrophy of the mammary glands is brought about by some secretion produced during pregnancy, which neutralizes the tendency of the cells to discharge under the influence of secretion from the pituitary and other organs. When this inhibitor is removed, the hormones causing the discharge of the gland come into action, and so cause the secretion.

This seems likely from the experiments of Mackenzie, who states that by injecting extracts of fœtus or placenta together with pituitary extract into a lactating animal, the action of the pituitary is inhibited.

In regard to the corpus luteum, there is a theoretical discrepancy between the views of those who regard the body as one of the building-up factors, and the results of Schäfer and others who find that corpus luteum extract produces an immediate secretion.

Hammond finds, as did previous observers, that the galactagogue effect of pituitary extract is only temporary. The effect is not muscular. The daily yield is only slightly increased, and is not dependent on increased blood-pressure. *The pituitary gland seems not to be the origin of the ordinäry changes in the mammary gland.* Histological evidence points to a direct action of the extract on the glandular epithelium. The milk obtained after injection has a higher percentage of fat than normal; in the subsequent milkings, however, there is a drop in the percentage of fat, although that of the other ingredients remains normal.

While the proteins, lactose, and ash are secreted in close connection with the water of the milk, the amount of fat is not so connected with the amount of water. The ratio of "nitrogen to lactose" is relatively constant throughout.

Hill and Sutherland Simpson state that pituitary extract

increases the immediate secretion of milk, but causes afterwards a decrease below normal.

(*b*) *The Kidney.*—The diuretic action of pituitary extracts was discovered by Magnus and Schäfer. The increase of secretion is accompanied by dilatation of the renal arteries, so that the organ swells. The action is, therefore, different upon the renal vessels from that on the arteries in general, which are strongly contracted by it. The rise in blood-pressure produced by this general contraction is not the sole cause of the increased secretion of urine, for a second dose administered a short time after the first will again accelerate secretion, although the second dose may not cause any rise of general blood-pressure, but rather a fall. There is, therefore, a specific diuretic effect upon the renal epithelium, just as there is upon the epithelium of the mammary gland. The tolerance produced by a first injection is then less marked than in the case of the blood-pressure response, but with large doses it is well marked.

It is reported that, under certain circumstances, there is a secondary diminution of the flow of urine, following upon vasoconstriction of the kidney.

Hoskins and Means believe that the pituitrin diuresis is due primarily to direct stimulation of the renal cells—usually aided, perhaps, by a concomitant vasodilatation in the kidneys.

(*c*) *The Stomach.*—It was shown by Edkins that extracts made from the pyloric mucous membrane in boiling water or 0·4 per cent. hydrochloric acid contain an active substance which, on injection into the bloodvessels of an animal, leads to a secretion of gastric juice.

Frouin found a similar action on the injection of gastric juice. Eirenhardt confirmed the results of Edkins, but Emsmann obtained some definite effects upon the flow of gastric juice as a result of injection of extracts of other organs, such as the intestine.

Houssay has recently reported a very decided action of pituitary extracts upon the flow of gastric juice, and has published some very convincing tracings. This appears to be a direct action on the secreting cells, as in the case of the mammary gland and the kidney. At any rate, the effect can be observed upon the isolated stomach.

6. *General Physiological Effects (Subcutaneous and Intravenous Injections)*

In 1899, Schäfer and Vincent reported that they had made a few experiments upon the effects which can be produced by the subcutaneous injection of decoctions of the infundibular part of the pituitary body. These were performed upon mice and young rats, and, although the dose required was much greater, showed that the pituitary extracts can produce results resembling in a general way those of adrenal extracts. They cause quickened respiration, increased heart's action, and ultimately paralysis, beginning in the hind-limbs.

Similar experiments have since been carried out by many observers. Diuresis, hæmaturia, and albuminuria have been recorded. Etienne and Parisot further record a permanent hypertension as the result of repeated injection of pituitary extracts.

It is stated that the effects of subcutaneous injection are modified by previous injection of thyroid extract, or extract made from the anterior lobe of the pituitary body or the pharyngeal pituitary.

The toxic effects of pituitary extracts are not nearly so pronounced as those of the adrenals. The symptoms observed, in addition to those mentioned above, are apathy and somnolence, excitation followed by muscular weakness, sudden cessation of heart-beat, and loss of weight after repeated injections, cardiac hypertrophy, ulceration, and hæmorrhages in the intestine, and hyperæmia and hæmorrhages in the kidney.

Urechia found that a reinjection after an interval of ten days gave rise to symptoms of an anaphylactic nature.

E. The Question as to which Elements of the Pituitary Body furnish the Active Substance or Substances —Functions of the Different Parts of the Pituitary Body

As we have already seen, Howell discovered that it is from the posterior lobe only that active extracts can be obtained. This was confirmed by Schäfer and Vincent. The observation was contrary to what might have been expected, since, from the distinctly glandular nature of the anterior lobe, it would appear

à priori that it would be more likely to furnish active physiological substances.

But we must remember that there are epithelial elements in, and in close relation to, the nervous portion (Figs. 94 and 95), and it was a natural assumption that these, and not the nervous portion proper, would be found to yield the pressor substance. But some years ago, Professor Osborne and myself tested the matter, and found that an extract made from the central part of the infundibular portion—devoid of epithelial elements—is much more active than one from the peripheral epithelial part. We expressed the opinion that probably the external layer would be found to be inactive if it could be obtained quite free from admixture with the central portion. Schäfer and Herring found this to be the case too with the substance which acts as a diuretic. Improbable, then, as it would appear at first sight, the conclusion is inevitable that it is the nervous portion proper which contains the substance or substances having such pronounced pharmaco-dynamical properties, different from those possessed by other kinds of nervous tissue.

I have never had an opportunity of repeating the experiments carried out in conjunction with Professor Osborne, but, since they have been amply confirmed, I am strongly inclined to adopt the view of Houssay that *the substance or substances are secreted by the cells of the pars intermedia, and then collected and concentrated, or changed into more active forms in the nervous portion proper.*[1]

No physiologically active substances can be extracted from the anterior lobe (except a depressor substance, which is common to all organs and tissues). This part of the pituitary is related to the general growth of the body, and especially of the skeleton. (See Section F.)

F. Feeding and Metabolism Experiments

The first metabolism experiments were performed by Schiff.

[1] Herring has recently confirmed the results of Osborne and Vincent. "The pars nervosa is from two to five times more powerful than the pars intermedia in its action." He thinks that the substance acting upon the uterus is formed at an early stage in the pars intermedia, but the substance acting upon the blood-pressure and kidney is a later product, resulting from the breaking down of the hyaline bodies or disintegrating pars intermedia cells in the pars nervosa.

He found that there was no influence on the nitrogen in any case, but that the phosphorous output was sometimes increased, due to katabolism of bony tissue. But the increase may have partly been due to nuclein.

Moraczewski found in a case of acromegaly that the nitrogen output was increased, also that of phosphorus, while Oswald found no effect on nitrogen or phosphorus.

Malcolm noted that the anterior lobe, administered dry, tends to cause a retention of nitrogen; the dried nervous portion has a similar effect. The fresh entire gland, in large doses, increases the output of nitrogen. The anterior lobe causes a retention of phosphorus, while the posterior lobe causes a loss followed by retention. On the whole, Malcolm's results pointed to a greater activity on the part of the nervous portion.

Caselli observed no effect on growth from long-continued injections of extracts made from the whole gland, but in some cases feeding with the gland retarded growth. Sandri fed young mice and guinea-pigs with pituitary emulsion, and states that this caused an arrest of growth. Cerletti injected pituitary emulsion intraperitoneally into young animals, and found that the animals receiving the injection fell uniformly below the controls in weight, and that the bones of the animals receiving the emulsion were, as compared with the controls, somewhat shorter as regards the diaphyses, but longer as regards the epiphyses.

Schäfer has carried out a series of feeding experiments on white rats, the general conclusion from which is that the addition of small amounts of pituitary tissue to the diet of rats has little or no effect upon growth.

Franchini, working with rabbits and guinea-pigs, reports that the calcium and magnesium metabolism is much reduced. Elfer reports that subcutaneous injection of pituitary extract does not affect the protein metabolism, but induces a temporary retention of phosphorus, calcium, and magnesium.

Quite recently Rosalind Wulzen has investigated the effects of administration of anterior lobe of pituitary body to young growing birds. A very distinct effect is shown in the direction of retardation of growth, which is manifested both in the body and in the length of the long bones. Involution of the thymus accompanies this retardation, and the suggestion is made that

the former may bear a causal relation to the latter. The effects are more marked in males than in females.

In very few of these investigations (the last-mentioned series forming a notable exception) has sufficient attention been paid to the difference between the anterior and posterior lobes of the pituitary. It must be pointed out that, even when ordinary care is taken to separate the anterior from the posterior lobe, the former will include a strip, which varies in thickness in different animals, of the pars intermedia. The reflection of this part over the nervous portion is now well known, and account has been taken of its presence in the consideration of the effects of posterior lobe extracts (see Section D), but the fact which I have just pointed out, viz., that there is a reflection of the pars intermedia over the anterior lobe, is not so generally recognized (Fig. 94). If the pars intermedia be traced round from the nervous on to the glandular portion, it will be noticed that the cells forming it gradually fuse with the cells of the glandular portion in the depth of the latter structure, but are continued as a layer, retaining at any rate some of the characters of the pars intermedia, along the edge of the cleft. Although the amount of pars intermedia adhering to the anterior lobe is not very considerable, it is possible that it might make a difference to the physiological extract.

Houssay is the only author, so far as I am aware, who has definitely drawn this as a continuation of the pars intermedia; though Herring states that the anterior lobe in the cat is separated from the cleft by cells, "which are larger than endothelial cells," and are continuous at the anterior and posterior ends of the cleft with the cells of the epithelial reflection. He admits too that the cells of the intermediate portion occasionally spread down a little over the front of the anterior lobe. The general arrangements are shown in Fig. 94, and the microscopical structure in Fig. 95.

Pituitary feeding is stated to have very similar effects to those produced by thyroid in bringing about precocious metamorphosis in amphibia. It is also said that the rate of fission of planarian worms is increased by a diet of pituitary substance.

G. Grafting Experiments

The effects due to increased functional activity of the pituitary body cannot be induced by glandular transplantation.

Cushing adopts the theory of W. S. Halsted that an existing "physiological deficit" is one of the essentials for a successful organo-transplantation. In support of this, Crowe, Cushing and Homans observed that the life of animals, after a total pituitary extirpation, could be prolonged by the immediate reimplantation into the cerebral cortex of the excised gland, which lived for a month.

In the absence of such a previously established deficit, the transplanted gland becomes absorbed in a short time. In Schäfer's experiments the only distinct effect noticed was with the posterior lobe, which caused a temporary increase in the flow of urine. As the implanted gland soon became absorbed, this result is probably to be looked upon simply as the effect of the administration of an equivalent amount of pituitary extract. It is possible, however, that the transplanted gland may have functioned for a short time.

In Exner's experiments on rats, transplantations were made of glands taken from young animals, and there was a temporary increase in growth and weight. But it is possible, in this case as well, to assume that the effect was comparable to a long-continued administration of an equivalent amount of extract.[1] It is pointed out by Cushing that the results of these various transplantation experiments suggest some therapeutic possibilities for this method, as the slow absorption of the secretion may be an effective means of administering the active principle. Cushing appears to have obtained some clinical evidence that, when a patient is actually suffering from a physiological deficiency, fragments of a transplanted pituitary body may survive and remain permanently active.

H. Stimulation of the Pituitary Body *in situ*.

Cyon has studied the functions of the gland by the method of direct excitation. He exposed the hypophysis by trephining the base of the skull beneath the sella turcica. Then he exerted light pressure upon the gland by means of a small pad of cotton. He observed immediately a considerable variation

[1] It must, however, be noted that the effects produced, viz., increase in growth and weight, are in a contrary sense to those observed by the majority of recent experimenters, administering the gland by the mouth. But the effect of giving whole gland would possibly be different from that of giving anterior lobe only.

in the blood-pressure and in the number and intensity of the heart-beats. These variations occurred to some extent as the result of the trephining, but were much exaggerated by a very slight electrical stimulation. Cyon worked with rabbits, and noted a considerable slowing of the heart-beat, with increase of amplitude.

Different results have been obtained by the majority of subsequent workers ; but Masay obtains results similar to those of Cyon, though his interpretation is different. The effect of direct stimulation of the gland he attributes to an increased discharge of the internal secretion into the blood-stream, where it produces the usual result due to the action of the extract upon the heart.

Schäfer reports that, in dogs, partial injury to the pituitary by means of a thermo-cautery or mechanical agents induces marked diuresis. This result is specially interesting in relation to the polyuria, which occurs in injuries and tumours affecting the base of the brain. This polyuria is more likely to occur when the pars intermedia is involved.

I. Extirpation Experiments

The first to perform experimental extirpation of the pituitary was Horsley, in 1886. Subsequent observers obtained contradictory results ; but it was established by Paulesco, in 1906, that the organ is essential for life, and that the onset of the acute symptoms depends on the loss of the anterior rather than on that of the posterior lobe. Paulesco's results have been confirmed in the main by Cushing and his co-workers. These find that puppies survive total extirpation longer than do adults ; that life can be prolonged (see Section G) by transplantation of the removed gland ; that, in all cases which recovered, a fragment of the anterior lobe was invariably found to have survived ; that animals with a fragment of anterior lobe, temporarily insufficient to support life, could be tided over a period of threatened cachexia hypophyseopriva by subcutaneous injections, or by feeding with anterior lobe ; and that removal of the posterior lobe leads to no very definite symptoms.

The acute symptoms observed were tremors, fibrillary twitching, arching of the back, insensitiveness, slow pulse and

respiration, a terminal abrupt fall in body temperature, and apathy passing into coma and death.

Cushing and his collaborators describe in animals, which recover after partial extirpation, certain constitutional disturbances, some of which (*e.g.*, carbohydrate tolerance) they now admit to be due in part to posterior lobe deficiency. These constitutional disturbances are adiposity, changes in the skin, disturbances of carbohydrate metabolism, of temperature, of growth, and of secretion by the kidney. Sexual inactivity and changes in most of the ductless glands are also described.

In some cases, the adiposity was so extreme that the weight of the animals became doubled, the deposition of fat is widely distributed, and in some regions œdema is recorded.

The skin becomes dense, dry, and less movable than usual. The hair becomes bristly and tends to fall out in patches—changes, as pointed out by Cushing, not unlike those found after thyroid extirpation.

When much pituitary substance has been removed, a subnormal temperature is the rule, and it may fall nearly to room temperature. The normal temperature may be restored by applying heat, but this hastens the end. In some cases, Cushing found, when the temperature was not very low, that it could be raised by ingestion, or subcutaneous injection, of pituitary extract. He states that a thermic reaction occurs, upon the injection of pars anterior preparations, only in cases of anterior lobe deficiency, and can be used as a clinical test when anterior lobe deficiency is suspected.

Pulse rate and respiration may be slow, and the blood-pressure low.

In young animals, partial pituitary extirpation results in disturbances of growth, especially in skeletal undergrowth.

Cushing also reports mental dulness, irritability, and a tendency towards epileptic fits.

After extirpation, a temporary glycosuria usually ensues, followed by a short period during which the assimilation limit is below normal. Subsequently, the animals acquire such a tolerance for sugar, that it is often difficult to produce alimentary glycosuria with the amounts of sugar that can be retained. According to Cushing's observations, these facts are connected with removal of, or damage to, the posterior lobe, and the interpretation given by this writer is as follows : " Normal posterior

lobe activity is essential to effective carbohydrate metabolism; an intravenous injection of posterior lobe extract produces glycogenolysis, and its continued administration in excessive amounts leads to emaciation. A diminution of posterior lobe secretion occurring in certain conditions of hypo-pituitarism (whether experimentally produced or the result of disease) leads to an acquired high tolerance for sugars, with the resultant accumulation of fat."

It is reported that, contrary to what might have been expected, removal of the posterior lobe increases the flow of urine rather than diminishes it. There is often a true diabetes insipidus, lasting for some time.

Experiments upon puppies disclose a persistence of sexual infantilism. There are as well changes in the testes, ovaries, thyroid, thymus and adrenal cortex and medulla. Moreover, changes occur in the reverse direction, for example in the pituitary after castration or thyroidectomy, and Cushing reports changes in the posterior lobe after extirpation of the pancreas.

So far as can be gathered from Cushing's account, this author attributes most of the disturbances above described to deficiency of the anterior lobe; indeed the only changes, which he definitely attributes to damage to the posterior lobe, are the effects upon carbohydrate tolerance and upon the secretion by the kidney. He does not state definitely whether these changes are due to loss of the nervous portion proper, or to that reflection of the pars intermedia which passes over the nervous portion.

Hanselmann and Horsley have failed to confirm the results of Cushing and his colleagues. In their experiments there was a very high death-rate from shock, hæmorrhage, and infection; but in the animals which survived, there were no characteristic symptoms like those described by Cushing. Hanselmann and Horsley further state that they observed a parallel death-rate in animals, in whom incomplete extirpation had been carried out. It is clear that the results of this series of experiments are quite different from those obtained by Paulesco and Cushing.

Aschner has opposed the view that the pituitary body is essential to life. He operates through the roof of the mouth. In adult animals, according to Aschner, there are no serious symptoms after the complete operation, although there are slight metabolic changes. In young animals, on the contrary,

profound effects are produced. In these cases, the symptoms described are analogous to those given by Cushing, and which are detailed above. His operative proceedings are criticized by Biedl and by Cushing.

Quite recently, Aschner has emphasized the relationships between the pituitary body and the genital organs, and points out the bearing of these upon pathological conditions in the human subject.

Staderini believes that extirpation experiments have given contradictory results in the hands of different observers, because operators have not always taken account of the "lobi laterales" and the "lobus premamillaris," described by him in the cat and in the ox. Perna has given a full description, with illustrations, of a "post-glandular prolongation" in the human subject. Other "accessory pituitaries," which may be mentioned here, are the "pharyngeal pituitary bodies" described by Haberfeld and others.

Complete extirpation can never be said to have been performed, unless these accessory bodies have been removed along with the main pituitary. Moreover, according to Biedl, total extirpation can only be described as such when, in addition to the removal of both lobes, the hypophyseal peduncle is severed as well. This latter operation is in itself, according to Biedl, as fatal as complete extirpation of the pituitary body. This was found to be the case also by Paulesco, and Aschner has only recorded the survival of animals in pituitary operations when not too much of the infundibulum was removed. Morawski, however, found that cutting through the peduncle has no serious effect on the monkey, while cats will not survive the procedure. This difference is explained by him by the fact that, in the monkey, cutting through the peduncle does not make an opening into the third ventricle, which must happen in cats and dogs. Biedl thinks that the real explanation lies in the anatomical relationships of the pars intermedia in the different animals, and is of the opinion that the opening of a communication with the third ventricle is a matter of no consequence.

Summing up, so far as is possible, these somewhat contradictory experimental results, we may conclude with some degree of probability that:—

1. Total extirpation of the pituitary body is a fatal operation, though the duration of life in the operated animal varies

very considerably according to its age. Adult dogs and cats will not survive more than two or three days; young animals may live as many weeks.

2. Partial extirpation of the pituitary body (if a small part of the anterior lobe be left behind) gives rise to disturbances in growth and metabolism already described, and these may be induced in young animals by deficiency of anterior lobe only.

3. The effects upon the genital organs may be due to deficiency of the pars intermedia, and the preponderance of evidence is that the polyuria and disturbance of carbohydrate metabolism (tolerance) are due to deficiency of this part as well.

4. It seems possible that removal of the nervous portion proper would be without any serious effects. This operation can, however, scarcely be carried out without damage to the pars intermedia, and this damage brings with it the metabolic disturbances just referred to.

It is interesting to note that, just as in the case of the adrenal body, so we have in the pituitary two main portions, one of them glandular, the other nervous. In the case of both organs, the physiologically active substances are found in the nervous portion (neurohypophysis, adrenal chromaphil tissue), while the glandular portion seems to be that which is essential to life.

The above summary represents the views of the majority of those who have devoted themselves to the subject of pituitary extirpation. But it is somewhat disconcerting to find careful observers who express themselves in such a sceptical vein as do Camus and Roussy. These authors believe that the polyuria which occurs on extirpation of the pituitary is not due to the removal of this organ, but to a lesion of the opto-peduncular region at the base of the brain. This region lies at the level of the grey substance of the tuber cinereum in the vicinity of the infundibulum. This zone seems to play some part in the mechanism of water retention in the organism. Atrophy of the genital organs and the "adiposo-genital syndrome" are likewise due less to any hypophyseal lesion than to trouble at some point in the base of the brain. The same applies to the changes in tolerance to carbohydrates and the appearance of alimentary glycosuria. These experiments, if the results are confirmed, will necessitate a reconsideration of our whole attitude in relation to the pituitary body.

J. The Question as to a Functional Relationship between the Pituitary and the Thyroid Bodies

From the time when the ductless glands first began to be known, there has been a decided tendency to regard them as physiologically more or less related to one another. In the earliest days, there can be little doubt that the grouping together of these organs was very largely to be ascribed to our uniform ignorance of their functions. But during recent years a certain amount of information has been accumulated, which renders it probable that there are true interrelationships between certain of the glands endowed with the power of internal secretion. The whole question constitutes a very fascinating, albeit a very abstruse, chapter in the physiology of internal secretion. We are, however, in this place concerned only with a possible functional relationship between the thyroid and pituitary bodies.

Many of the suggestions which have been made were of an *à priori* character. Cyon has put forward a theory of an elaborate kind about the mutual function of the thyroid and pituitary bodies, and he regards the latter as a centre from which the vascular supply of the brain is influenced through the former.

Rogowitsch, in 1888, observed in rabbits, killed at periods of from two to ten weeks after thyroidectomy, a marked hypertrophy of the pituitary body. This result was confirmed by many observers.

Quite recently Lydia M. Degener has found that the increase in weight of the pituitary, after the thyroid glands have been "completely removed"[1] from rabbits, runs parallel with the time which intervenes between thyroidectomy and the death of the animal. After an interval of 179 days, the pituitary body had increased to about three times the normal size.

In these hypertrophied pituitaries there is increased activity of the cells of the pars intermedia, and in the proper nervous part of the posterior lobe. In these situations, granular,

[1] This means, presumably, that the thyroid and internal parathyroid on both sides were removed, leaving behind both external parathyroids.

hyaline, or colloid bodies become very numerous ; they appear to be partly of a cellular nature and to find their way between the ependyma cells into the infundibular recess and ventricles of the brain. The colloid appears to arise from the epithelial cells of the pars intermedia.

The precise nature of the relationship existing between the thyroid apparatus and the pituitary body is by no means clear. Simpson and Hunter report that complete removal of the thyroid gland in lambs does not lead to the appearance of iodine in the pituitary. On the assumption that the iodine containing substance of the thyroid represents its active secretion, this does not support the Rogowitsch theory that, in thyroid insufficiency, the pituitary vicariously takes on its function. In the experiments of Simpson and Hunter, there was, however, some compensatory hypertrophy of the pituitary body.

It only remains to make reference to some experiments of Masay in opotherapy, with the object of ascertaining whether pituitary extract can replace the internal secretion of the thyroid ; the results were entirely negative.

K. **Pituitary Insufficiency and a Pituitary Antiserum or Cytotoxin**

Masay has attempted to produce pituitary insufficiency by the method employed by Demoor and Van Lint in order to obtain an "anti-thyroid serum." Guinea-pigs were injected intraperitoneally with an emulsion of dog's pituitary at intervals of two days. After three, four, or five injections the blood of the guinea-pig was collected and centrifugalized, and the serum (about 10 c.c.) was injected under the skin of a dog. Masay gives his results in considerable detail, and the effects upon the animal are shown in a series of illustrations. After a certain number, usually two or three, of such injections the dogs show symptoms, such as loss of flesh, muscular weakness, especially in the hind limbs, changes in the skeleton and in the structure of the pituitary, the symptoms constituting, according to Masay, a veritable cachexia hypophyseopriva.

Ossokin reports that the "hypophyseolytic serum," prepared from the blood of dogs immunized with posterior lobe of

pituitary, produces a marked fall of blood-pressure. The precise significance of this is difficult to understand.

It is yet too early for us to be able to determine the value of these antiserum experiments.

L. Chemistry of the Pituitary Body

Schäfer and Vincent, who described a pressor and a depressor substance, found that the latter could be separated from the former, on account of the fact that it is soluble in alcohol, in ether, and in normal saline solution. This is of course the depressor substance common to all animal tissues.

Schäfer and Herring contend that two active principles exist in pituitary extracts, one acting on the circulatory system, the other specifically on the kidney. Dale does not consider the evidence on this point to be satisfactory.

Within recent years three observers have claimed to have obtained, apparently independently, the active substance in a pure form. Houssay, in 1911, prepared the active substance as follows :—" The fresh hind lobes were boiled in water ; the filtrate was then precipitated with lead acetate and sulphuric acid, filtered, and the filtrate dried *in vacuo*. The residue is washed with chloroform, ether, and alcohol, and finally crystallized *in vacuo*. The product is insoluble in alcohol, ether, or chloroform, but very soluble in water, and is dialysable. It is precipitated by picric acid, platinum chloride, etc. If burnt on platinum foil, it gives off the smell of burnt feathers."

Solutions of this product in normal saline produce the effects of pituitary extracts upon the heart and vessels.

Fühner claims as well to have isolated a pure crystalline basic substance, which has been put upon the market in the form of its sulphate, and is called *hypophysin*. Fühner's product is said to possess all the activities of pituitary extracts on respiration, blood-pressure, and the uterus.

Herzberg has tested Fühner's substance clinically, and reports that its action upon the uterus is powerful and prompt. " Hypophysin " is stated to consist of four separate substances.

In still later papers, Fühner and Schickele declare that the substance acting upon the uterus is independent of that acting upon the blood-pressure, and can be obtained from extracts of the anterior as well as of the posterior lobe.

Robertson states that he has succeeded in isolating from the anterior lobe a substance called *tethelin* which quickens growth in young animals and is thought to have a possible value in hastening the healing process in wounds.

M. The Comparative Physiology of the Pituitary Body

Professor Osborne, working in conjunction with the present writer, showed that extracts of the pituitary body of the cod produce effects upon the heart and bloodvessels similar to those of extracts of the mammalian posterior lobe.

Schäfer and Herring demonstrated that extracts made from the cod's pituitary produce kidney dilatation and diuresis when injected, just as do extracts from the mammalian posterior lobe.

The subject has been recently more thoroughly investigated by Herring. This observer finds that the posterior lobe of the pituitary body of the fowl produces an effect on blood-pressure, kidney volume, and urine secretion, which is very similar to that produced by extracts of the posterior lobe of the mammalian pituitary. It was found to be impossible to determine whether the active principles in the posterior lobe of the bird's pituitary are products of the epithelial cells of the pars intermedia, or are formed solely in the nervous substance. No distinct effects were produced by extracts of the avian anterior lobe.

In regard to Teleostean fishes, extracts of the anterior lobe proper—chromophil portion of Sterzi and Gentes—have little physiological effect. The general effect of extracts of the posterior lobe is similar to that brought about by extracts of the mammalian and avian posterior lobes. In Teleosts the cells of the pars intermedia predominate in the posterior lobe, and are inseparable from the pars nervosa, so that one cannot determine which produces the active material. According to Herring, both are probably concerned, for wherever cells of pars intermedia—chromophobe cells of Sterzi—are bound up with pars nervosa, extracts of the resulting tissue produce the effects on blood-pressure, kidney volume, and urine secretion which have been associated with extracts of the posterior lobe of the mammalian pituitary. Extracts of the saccus vasculosus are practically inactive, and Herring supports the supposition

of Gentes that this structure has a function similar to that of a choroid plexus.

The Elasmobranch pituitary, as we have already seen, is quite different in structure from the pituitary bodies of mammals, birds, and Teleosts. There is no differentiation into anterior and posterior lobes. According to Herring, there are no cells precisely corresponding to those of either the anterior portion or the pars intermedia of the mammalian body. The presence of the true nervous portion seems also doubtful. Extracts of the Elasmobranch pituitary give rise to no characteristic physiological effects.

N. Diseases of the Pituitary Body

1. *Introductory*

According to Cushing, a pronounced constitutional dyspituitarism is not incompatible with a tolerable state of health and comfort. In regard to symptoms due to each of the two lobes, there may be an overaction or underaction of one lobe only, or an overaction of one lobe associated with insufficiency of the other. In the minds of many authorities the subject is rendered still more complex by a tendency to regard every disorder of the ductless glands as a polyglandular disease. This is said to be sometimes so pronounced as to make it doubtful which of the organs is primarily at fault. It is generally believed that derangement of any one of these correlated glands leads to disturbances in others, but a primary disorder of any one will produce its own special symptoms.

A functional hyperplasia of the pars anterior promotes tissue growth, chiefly shown in the skeleton, skin, and subcutaneous tissues, and at the same time there is an excitatory effect on the reproductive organs, as seen in the secondary sexual characters. On the other hand, insufficiency of the anterior lobe inhibits skeletal growth and sexual development.

Little is known about functional hyperplasia of the posterior lobe. This part seems to be concerned with tissue metabolism. Insufficiency gives rise to slowed metabolic processes. There is a high tolerance for carbohydrates, which are stored as fat, there is drowsiness, slow pulse and respiration, subnormal temperature, low blood-pressure, etc. This complex of symptoms just described strikingly resembles the phenomenon of hiberna-

tion, in which there is markedly slowed metabolism and in which histological changes in the pituitary body have been described.

There is a tendency for pituitary diseases to lapse into a condition where glandular insufficiency is the most noticeable feature, and this is especially the case with disorders of the anterior lobe.

Cushing divides symptoms of pituitary disorder into three main groups :—

1. Endosecretory symptoms on the side of hyperpituitarism.
2. Endosecretory symptoms on the side of hypopituitarism.
3. Endosecretory symptoms of a polyglandular character.

As one might expect, many and very complicated systems of classification have been attempted.

2. *Acromegaly*

(1) *Introductory*

The disease, which is characterized by enlargement of certain bones of the body, especially of the hands and feet, was first described by Marie, of Paris, in 1886. It was observed by Marie that the disease is associated with tumours of the pituitary body. It had, however, been described previously under other names, as "hyperostosis of the entire skeleton" by Friedreich, as "general hypertrophy" or "makrosomie" by Lombroso, as "giant growth" by Fritsche and Klebs.

(2) *Symptoms*

There is usually a history of definite symptoms before the characteristic deformities occur. Headache, pains in other parts, irritable temper, moroseness, loss of memory, disturbances of vision, increased appetite, thirst, and polyuria are enumerated among the early symptoms. In women amenorrhœa is frequently noted, while in men there may be loss of sexual power.

The head increases in size, the brows become arched and prominent, the forehead retreating. The nose is large. The zygoma and malar prominences are exaggerated. The upper jaw is not much altered, but the lower is distinctly enlarged (Fig. 98). The lower teeth may project beyond the upper. The chin is thick and the face may be oval or square. The tongue becomes enlarged and may force the mouth open and plays a part in the deformity of the alveolar processes. It is usually indented at the sides and the papillæ are enlarged.

FIG. 98.—Typical acromegalic profile. (From Cushing.)

The thorax is enlarged, especially from back to front. There are various degrees of kyphosis, scoliosis and lordosis.

The hands are increased in size, the fingers are thick and sometimes sausage-shaped. Though the bones of the hand are sometimes increased in length, most of the enlargement is in the subcutaneous tissue, with increase of the points of attachment of the tendons. (See Fig. 99.)

The ankles and feet are decidedly enlarged. The skin is usually dry, but perspiration is easily induced. Flushing tingling and other vasomotor changes are frequent. In the later stages the muscles become small and weak, a change which accounts for the peculiar position of the head, the kyphosis, and other deformities.

FIG. 99.—Characteristic square hand with deep palmar creases. (From Cushing.)

Affections of sight are common, blurring of vision, concentric narrowing of the visual field, bitemporal hemianopia, optic atrophy are often met with. The pupils may be dilated. The sixth and third nerves may also be affected. Painful noises in the ears are frequent and deafness may supervene. Loss of memory, mental slowness, depression or delusions

are frequent. Somnolence is often marked, and may pass into stupor. The urine is normal or there may be glycosuria (Dock).

(3) *Ætiology and Onset*

Acromegaly has been sometimes ascribed to syphilis, or some other specific infection. Heredity has also been claimed as having some part in the causation. There is, however, no sufficient evidence that any of these bear any essential relation to the disease.

The disease occurs, perhaps, most frequently in early adult life, between the age of puberty and the thirtieth year. It is more common in women than in men. The onset is gradual.

(4) *Metabolism in Acromegaly*

If acromegaly be, in fact, due to a hypersecretion of the pituitary body, we should naturally expect that in this disease the metabolism would be modified in the same direction as in animals fed upon pituitary substance. The few experiments which have been performed upon acromegalic patients have given contrary results. Retention of phosphates in the bones and muscles and increase of urinary calcium have been alleged.

(5) *Morbid Anatomy*

The bones appear to undergo a true hypertrophy in the majority of cases, though it is stated that the superior maxillary appears to be larger on account of a simple dilatation of the antrum. In the long bones the enlargement affects the ends as well as the shaft.

The view which has the greatest number of adherents at the present time is that the characteristic lesion in acromegaly is adenoma of the pituitary. This belief was first definitely put forward by Benda. Previously the tumour had been known by various names, perhaps most frequently as a "round-celled sarcoma." Hanau had previously suggested that the typical growth is an adenoma; and Löwenstein has given a lucid account of the development of this adenomatous tumour.

Other tumours of the pituitary do not appear to give rise to acromegaly. Thus, Pende states that tumours of the "pharyngeal pituitary" (remains of the pituitary duct) never

give rise to acromegaly. Several authors report cases of pituitary sarcoma without any signs of acromegaly. The same applies to carcinoma and endothelioma.

Microscopical examination shows that the tumour in acromegaly has all the characters of the anterior lobe of the pituitary body. The various kinds of cells found in the latter structure are also regularly found in the tumour.

Thus, it would appear that an adenoma of the anterior lobe of the pituitary is the essential lesion characteristic of acromegaly.

(6) *Pathogeny*

Various theories have been sustained as to the origin and essential cause of the symptoms of typical acromegaly. It was suggested by Freund that acromegaly is simply an anomaly of development. Some writers have imagined that the essential lesions in acromegaly are in the thyroid or in the thymus. It has also been suggested that defects in the reproductive organs may be responsible for the conditions (*vide infra*, p. 375). The nervous system has from time to time been called in question. But of late years most of the theories advanced have assumed that the pituitary is in some way affected in all undoubted cases of acromegaly.

Of the pituitary theories, the first was that of the original describer of the disease—Marie. His view was that acromegaly is due to destruction of the pituitary, and therefore to complete abolition of its function. Those who still uphold this view look upon the gland as supplying a hormone which regulates the growth of the skeleton, which growth, in the absence of such regulation, proceeds abnormally. Bleibtreu has published a record of a case of acromegaly, in which he states that there was total destruction of the pituitary gland.

The opposite view, that the symptoms of acromegaly are due to a hypertrophic condition of the pituitary, more particularly of its anterior lobe, is held by Tamburini and Woods-Hutchinson. The most important argument in favour of this view is the frequency with which a true adenoma has been reported as occurring in typical cases of acromegaly. It may be supposed that, according to this theory, the anterior lobe

of the pituitary body furnishes an abnormal, an excessive, quantity of some hormone which stimulates bone growth, and that, in consequence, the growth of bone itself becomes excessive.

The cases referred to above in which after death the substance of the pituitary has been completely destroyed and replaced by a malignant growth, would seem to present a certain difficulty in the way of acceptance of the hypersecretion theory. They would seem, in fact, to furnish important evidence that the symptoms of acromegaly have been brought about as the result of the suppression of an internal secretion. But, of course, it is possible to assume that the tumour at its beginning was non-malignant, and that the malignant character has become developed shortly before death, and that death has resulted from entire suppression of the function of the gland, owing to destruction of the normal glandular cells by those of a malignant nature; for it appears possible that complete destruction of the gland is incompatible with continuance of life.

Since, after destructive disease of the reproductive organs, the pituitary is found to be enlarged, it has been suggested that the actual commencement of the mischief in acromegaly may be in the ovary or the testis.

The pathogeny of acromegaly thus appears to be analogous to that of exophthalmic goitre, the first being due to a hyperfunction of the pituitary, the second to a hyperfunction of the thyroid gland.

Yamada has recently reported a case in which there were clear symptoms of acromegaly with a normal pituitary, but the thyroid was enlarged, the thymus was persistent, the testes atrophic, the pineal contained masses of colloid, and there was hypertrophy of adrenal medulla. The case was therefore characterized as "polyglandular." We must bear in mind the recent experiments of Camus and Roussy (see above, p. 365).

(7) *Course and Event of the Disease—Diagnosis, Prognosis, and Treatment*

The disease runs a slow and prolonged course, and goes on to a fatal issue.

The diagnosis is usually a matter of no great difficulty.

From *osteitis deformans* and from *arthritis deformans* it may be distinguished because the enlargement is general, instead of affecting only the shaft, as in osteitis deformans, or the ends, as in arthritis deformans. In osteitis deformans, too, as pointed out by Marie, the face is triangular, with the base *upward*, while in acromegaly it is ovoid, with the large end downward. In congenital progressive hypertrophy, or "giant growth," only one limb becomes affected, and the shaft of the bone is involved.

But the differential diagnosis from certain diseases of the nervous system, and in particular from *syringomyelia*, is stated to be sometimes very difficult, or even impossible.

In affections of the spinal cord enlargements of the extremities are liable to occur, and especially is this true in syringomyelia. Fischer gives several examples from Schlesinger and others. It is stated that syringomyelia may give rise to the typical clinical and anatomical features of acromegaly. If this is true, then it will be absolutely impossible in certain cases to make a correct diagnosis during life, and it must have frequently happened that cases of syringomyelia have been described as "acromegaly without tumour of the pituitary." The suggestion has been tentatively put forward that the hypersecretion of the pituitary may, after all, produce the condition of acromegaly by action upon the nervous system.

The prognosis is bad, and all treatment hitherto attempted seems to be without avail. Naturally, treatment with pituitary preparations has been tried. This, of course, has been done on the hypothesis that acromegaly is due to diminished action on the part of the gland. The results are unsatisfactory, and even definitely unfavourable results were sometimes obtained. No reduction can be effected in the size of the extremities by internal administration of the gland. Magnus-Levy records a case of acromegaly treated with pituitary substance. Symptoms arose which recalled features of Graves's disease—marked perspiration, polyuria, and alimentary glycosuria.

It seems, from all that has gone before, that the only rational treatment for acromegaly is a partial extirpation of the pituitary body. This was first definitely suggested by Victor Horsley, and has been extensively carried out by Cushing and others.

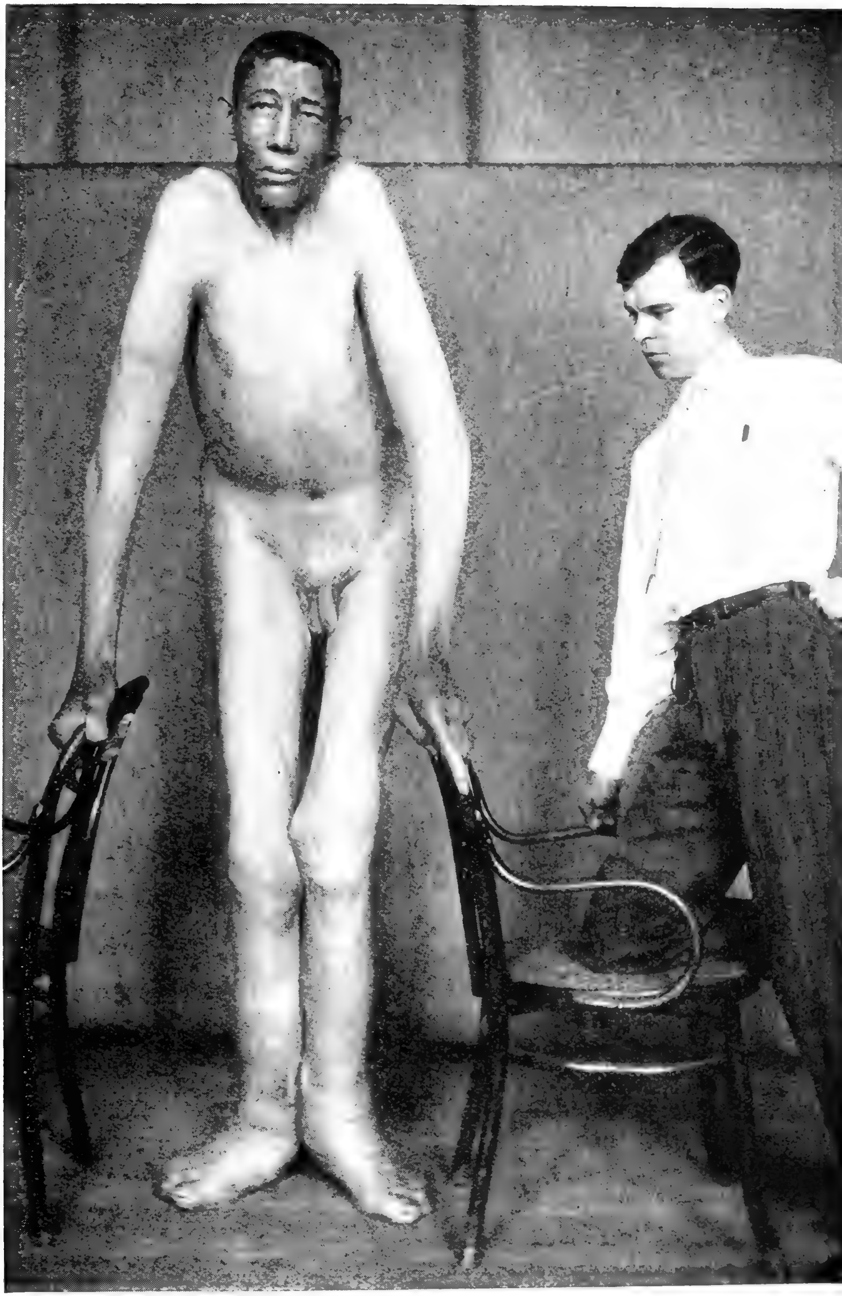
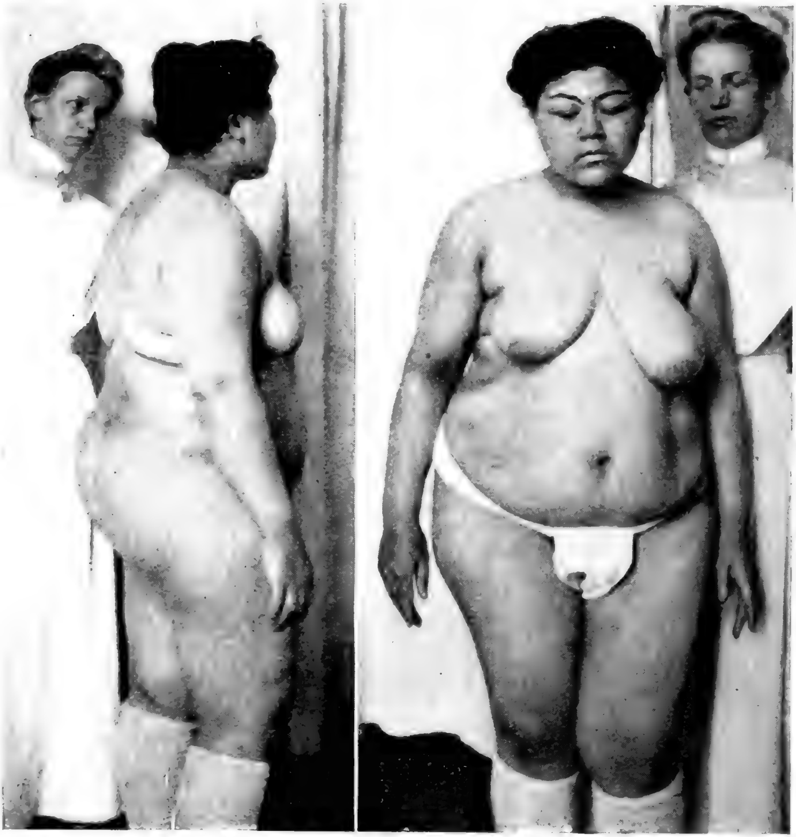


Fig. 100.—Hyperpituitarism with giant overgrowth. Note the narrow chest, large joints, hypotrichosis; also large size of hands compared with Dr. Crowe, whose height is 5 ft. 8 in. (From Cushing).

(8) *Other Conditions involving Pituitary Hyperfunction*

There are reasons for thinking that many forms of gigantism are due to hyperfunction of the pituitary, and probably to hyperfunction of the anterior lobe. In these cases there is rarely, if ever, a definite adenoma of the gland. But it is



Figs. 101 & 102.—Marked adiposity. 124 lb. increase in 14 months. (From Cushing.)

possible that the structure might manufacture certain substances in excess of the normal, without overgrowth of the gland as a whole, but simply by multiplication of certain cells.

3. *Conditions involving Hyposecretion of the Pituitary*

Fröhlich was the first to point out that in cases of pituitary

tumour without acromegaly there may be manifested a peculiar syndroma, characterized by the accumulation of fat and disturbance of the genital functions—*degeneratio adiposo-genitalis.* Erdheim, however, is of the opinion that not only pituitary tumours, but other growths in this region of the base of the brain, may give rise to a similar train of symptoms. Cf. Camus and Roussy, p. 365. It is thought by Fischer that the effects are due to damage to, or destruction of, the posterior lobe of the pituitary body. The experiments of Cushing, however, would seem to teach that it is deficiency of function of the anterior lobe which leads to degeneratio adiposo-genitalis.

FIG. 103.—Typical case of Infantilism of Lorain type with an enlarged 2 cm. sella. Patient aged 20 years 6 months. Height 4 ft. 4 in. (after Cushing.)

Dystrophia adiposo-genitalis (*Degeneratio adiposo-genitalis*).—This condition, sometimes known as Fröhlich's syndrome, is very generally supposed to be due to pituitary insufficiency. The patient becomes obese and the fat has a peculiar distribution. It is most abundant on the abdomen, buttocks and the proximal portions of the extremities. (Figs. 101 and 102.) Dwarfism is a common condition, due to deficient skeletal development. The genital organs remain in the infantile state and the secondary sexual characters do not develop. The skin is in most cases thin, smooth, and soft.

Infantilism.—This term was first used by Lasègne and the types generally recognized are those of Lorain, Brissaud, and Variot and Pironneau. Lorain's type is an infantilism in which the proportions are like those in the adult and there is a hypoplasia of heart and arteries. (Fig. 103.) Brissaud's type was that due to thyroid deficiency and called the myxœdematous type. Variot and Pironneau propose adding another type—*progeria.* Gilford proposes the following classification :—

Infantilism.

1. Evolutionary or phylogenetic infantilism

2. Developmental or ontogenetic infantilism
   - A. Infantilism of cells
   - B. ,, ,, organs
   - C. ,, ,, the individual as a whole

Class I. Symptomatic General Infantilism
Infantilism as a fluctuation

- *A.* Toxic
- *B.* Correlative
  - (*a*) Endocrinous
  - (*b*) Simple correlative
- *C.* Deprivational of mixed causation

Class II
Essential Infantilism
Infantilism as a mutation

- Ateleiosis
  "continuous youth"
- Progeria
  Infantilism
  "Senilism"
  Premature old age

(Cushing thinks these two are possibly pituitary diseases.)

Mr. Hastings Gilford believes that only one form of infantilism has been absolutely proved to be due to a deficiency of internal secretion, and this is *thyroid infantilism.* This is frequently referred to as myxinfantilism (Brissaud's type). This author sees no objection to the use of the term "pituitary or Fröhlich's infantilism," but thinks that we are not yet justified in affirming finally that it is the result of a deficiency of pituitary hormones.

Cushing includes the Lorain type as of pituitary origin.

Gilford thinks that many forms of infantilism are due to quite other causes than deficiency of internal secretion. Thus *ateleiosis* (delay of development, sexual organs being most delayed) is a mutation, and as such is liable to be associated with other anomalies of development—such as those of the thyroid or pituitary. These are, however, secondary, and not the cause of the condition.

Achondroplasia (chondrodystrophia fœtalis).—Achondroplasic dwarfs resemble cretins, but shortness of the limbs is more noticeable in the former. According to some authors, the condition of achondroplasia is distinguished from chondrodystrophia, the former being due to hypofunction of the reproductive organs arising *in utero*, the latter being the result of hypofunction of the anterior lobe of the pituitary arising in fœtal life. The latter is sometimes a cause of brow presentation and dystocia. According to some writers, there is a diminution in size of the sella turcica, and pituitary extract should be tried. The patients are not benefited by thyroid treatment.

The condition has to be diagnosed from cretinism and rickets.

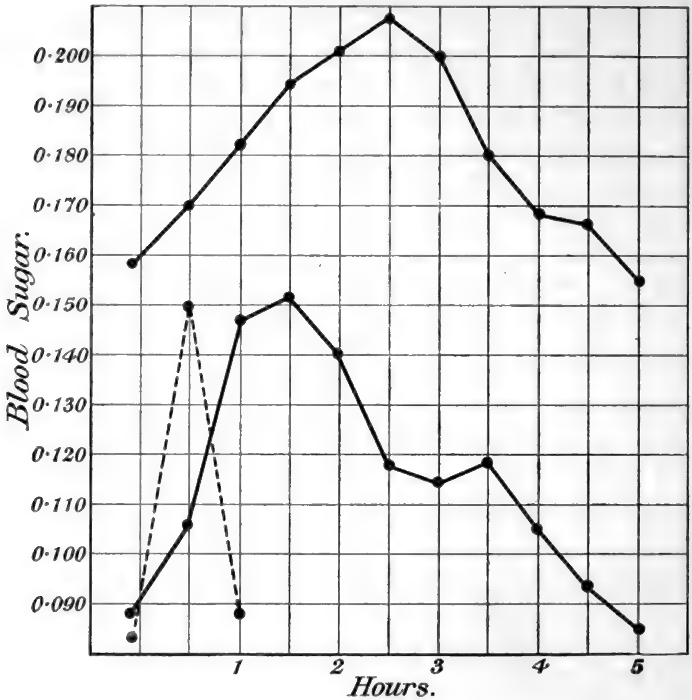
The disease is, in brief, a fœtal disorder which causes a defective growth of certain of the bones *in utero* and leads to congenital dwarfing of the extremities and other deformities which persist throughout life. It is said that there is an abnormal arrangement of the cartilage cells along the line of ossification.

The obscurity involving the condition is shown by the very numerous names which have been employed to describe it. In addition to the above-mentioned names, the disease is referred to as *Rachitis fœtalis*, *Pseudorachitism*, *Pseudorachitis fœtalis micromelica*, *Cretinoid dysplasia*, *Chondritis fœtalis*, *Micromelia*.

There is no certain proof that the typical cases of Achondroplasia arise from any disorder of any of the glands of internal secretion.

Carbohydrate Tolerance in Pituitary Disorder.—An increased tolerance for carbohydrate has been recognized for some years as a test for pituitary insufficiency. One of the recognized methods of conducting this test is as follows: Twenty-five, fifty, or a hundred grammes of glucose dissolved in 150 c.c. of

water are administered to the patient on an empty stomach. The blood-sugar is estimated after half an hour and then at intervals of one hour. The blood-sugar increases in amount up to a certain degree and then falls again. The curve obtained must then be compared with an average normal curve.



The chart illustrates the effect of 25 gms. of carbohydrate on a moderately severe case of diabetes. The interrupted lines represent a normal blood-sugar curve; the upper continuous curve was obtained when the patient was receiving a diet slightly in excess of his tolerance level for carbohydrate, the blood-sugar before the test being high in consequence. The lower curve was obtained after two days' starvation which had reduced his blood-sugar to a low level. In both the initial level was not regained till after 5 hours. (From Maclean.)

Diabetes insipidus.—The symptoms of this disease are too well known to require a description. The point of immediate interest to us is the connection between the polyuria and a disturbed function of the pituitary body. A considerable number of cases have been described in which a lesion of the posterior lobe was found *post mortem*. Such lesions are,

however, not invariably accompanied by diabetes insipidus. The experimental and pathological evidence is not conclusive.

Treatment of patients by means of subcutaneous injection of pituitary extracts seems to have given some very striking results. According to Kennaway there is very frequently an immediate restoration of a normal state of the urine when pituitary extract is given in diabetes insipidus. This writer also urges that the fact provides strong evidence for the normal activity of the gland in regulating the secretion of urine.

In pituitary disease conditions of primary over-activity become blended later on with symptoms characteristic of known stages of functional insufficiency. So that in certain conditions it may be difficult to tell which predominate (Cushing). It will be remembered that Tamburini in 1894 described a "two-stage" process in acromegaly; a glandular hypertrophy with hyperactivity characterizing the first stage, while in the second or terminal there occur degenerative changes with diminished activity and resultant cachexia.

O. The Use of Pituitary Extracts in Medicine, Surgery, and Gynæcology

Reference has already been made to the use of pituitary extracts in acromegaly. We have seen that they have not been found to be beneficial in this disease. Nor should we expect them to be of service if acromegaly be, in fact, due to a hypersecretion of the gland.

But there are many other conditions in which pituitary preparations have been recommended and employed.

In conditions of *shock*, pituitary preparations are believed to be of more value than adrenin. This is due partly to the fact that pituitary preparations ("pituitrin," "infundibulin," etc.) keep the blood-pressure raised for some considerable time, while the effect of adrenin is very fleeting. Saline infusions should, however, be used; reliance should not be placed on the pituitary extract alone.

Owing to its powerful action on the uterus (see p. 351), pituitary substance is now employed in many *obstetric conditions*. The action on the uterus was first noticed by Dale, and has since been studied by several observers. Foges and Hofstätter have obtained results similar to those of Dale and

Bell, and recommend pituitrin in post-partum hæmorrhage. Other observers now recommend the use of the drug in labour.

Bell strongly recommends "infundibulin" in cases of *sluggish intestinal peristalsis* and paralytic distension of the intestines.

It is probable, also, that the diuretic effect of pituitary extracts may be of clinical value. The value of subcutaneous injections of pituitary extracts in diabetes insipidus has already been noted.

CHAPTER XVI

THE FUNCTION OF THE PINEAL BODY

MUCH attention has been devoted to the pineal body from the standpoint of comparative anatomy. Its relationship to the pineal eye of lower vertebrates seems to have led to the conclusion, which may, after all, turn out to be premature, that the pineal body of mammals is a purely vestigial organ, and no longer of any functional importance. Notwithstanding the numerous investigations which have been carried out upon the comparative anatomy and development of the organ, there appear to be few careful and detailed descriptions of the microscopical structure in Mammalia. Moreover, the number of essays in the direction of a physiological study of the structure are not very numerous. The general appearance of the body on microscopical examination certainly suggests the possibility of a secretory function, and, as we shall see, there is some evidence that the pineal body controls in some way or other (possibly by means of an internal secretion) the early growth of the individual.

Anatomy and Development of the Pineal Body

The pineal body, or pineal gland (conarium),[1] is a small pinkish structure situated underneath the posterior region of the corpus callosum, and resting upon the anterior elevation of the corpora quadrigemina.

A section through the diencephalon of an early human embryo shows the "roof-plate" and the "floor-plate." At the posterior end of the former is an elevation, which forms a hollow evagination of the brain-roof—*the pineal process.* The distal extremity of this pineal process becomes enlarged to a

[1] The epiphysis of the mammal was known to the ancient Greek anatomists, Galenus described it as the "Σῶμα κωνοέιδες, Κωνάριον." Descartes, in 1649, as is well known, considered it to be the seat of the soul.

sac-like structure, which subsequently becomes lobed and solid. This is the *pineal body*. The proximal part of the evagination remains hollow, and forms the *pineal stalk*, and the whole structure, body and stalk, is usually called the *epiphysis* (McMurrich).

In the Reptilia and other lower groups of animals the outgrowth from the roof of the diencephalon is double, a secondary outgrowth arising from the base or from the anterior wall of the primary one. This secondary outgrowth—the anterior evagination—becomes elongated until it reaches the epidermis of the head, and here it develops into the *pineal eye*. In mammals this anterior process is not developed.

In addition to the epiphysial evagination another evagination arises from the roof-plate of the first cerebral vesicle. This is placed farther forward in the region which subsequently becomes the median portion of the telencephalon. This structure is called the *paraphysis*, and is found in the lower vertebrates and in the marsupials (Selenka), but up to the present time has not been found in other groups of the Mammalia. It is supposed to be comparable to a choroid plexus which is evaginated from the brain surface instead of being invaginated, as is usually the case. There is no evidence that a paraphysis is developed in the human brain (McMurrich).

Histological Structure of the Pineal Body

The pineal body is covered on its upper surface by the pia mater, which provides the connective-tissue skeleton of the organ, and carries the bloodvessels into the interior. This sheath of connective tissue sends in septa, which break up into a fine network in the parenchyma of the gland, and divide up the whole structure into "acini," or "follicles." (Figs. 104 and 105.)

Some writers state that there are no true septa, but irregular trabeculæ. It seems that in regard to the distribution of the connective-tissue frame-work of the pineal body there is considerable difference between different species and between different animals of the same species, but of different ages. In the connective-tissue cells a yellowish or brownish pigment is frequently found.

A number of cross-striated muscle fibres may be found in

connection with the connective-tissue elements. The connective-tissue septa and bands carry in numerous bloodvessels and nerves, of which some are doubly contoured.

The cylindrical epithelium of the ependyma not only covers the part of the pineal body which is nearest to the brain ventricle, but lines certain hollow spaces found within the body of the gland itself. The majority of these hollow cavities become obliterated by the proliferation of their lining cells.

There appear to be no true nerve cells in the adult mammalian body. It is stated that there are nerve fibres derived from the brain substance as well as sympathetic fibres, which enter, along with the bloodvessels, in the interior of the pineal body.

FIG. 104.—Section of the pineal gland of the sheep. (Drawn by Mrs. Thompson.)

The parenchyma of the gland is made up of follicles, which, however, are only sharply marked out at the periphery of the organ (Fig. 104). The cells of these follicles have sometimes been described as resembling those of adenoid tissue.

An exact description of the constituent cells of the follicles cannot be compiled from the accounts of the various writers upon the subject. It seems clear, however, that the cells are of two chief kinds—neuroglia and secretory cells. The latter are slightly stainable with a large oval granular nucleus. The cell body contains granules, either distributed throughout its substance, or arranged round the periphery. Galeotti described secretory processes in these cells.

The "brain-sand" ("acervulus cerebri") which occurs in certain follicles, has been known from the earliest times. It has not been shown to be of any physiological importance. It is found also in the choroid plexus and in the pia mater of the lobus olfactorius.

Cysts are also found in the pineal body.

Cutore has recently described a structure in the pineal body of the ox which is of doubtful significance. It is a rounded body of variable size in the roof of the diencephalon. It may

exist side by side with the *diaphysis* described by Favaro, and it is connected with a very distinct bundle of nerve fibres. This structure, which the author calls "corpus præpineale," appears to reach its maximum development in the later fœtal stages and the earlier period of extra-uterine life. After this it becomes reduced, and seems to be absent in the adult.

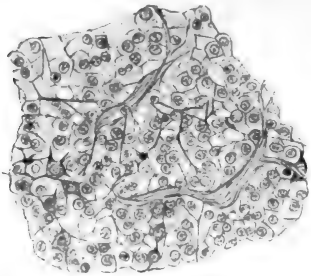


Fig. 105.—A small portion of the pineal gland of the cat, as seen under a high power of the microscope. (Drawn by Mrs. Thompson.)

Costantini calls special attention to the granular nature of the pineal cells, and concludes that the pineal body is an internally secreting gland. Similar conclusions have been reached by Galasescu and Urechia, who called special attention to the oxyphile cells of the gland.

Physiological Experiments upon the Pineal Body

1. *Injection of Extracts of the Pineal Body*

The first experiments in this direction were made by Howell in 1898. This author reports that glycerine extracts of the body produce sometimes a slight, sometimes a marked fall of blood-pressure. This observation has, of course, little or no bearing on the function of the organ. (See discussion in Chapter III.)

Cyon in 1903 made extracts from the pineal bodies of the ox and sheep, and tested their effects upon the heart and blood-vessels on intravenous injection. There was no effect upon the blood-pressure, probably because the dose was not large enough. The number of heart-beats was, however, increased, while the excursion was diminished. This is an effect similar to that obtained by stimulation of the true accelerator nerves. Such are the effects of small doses. With larger doses the heart-beats become stronger and less frequent, and also irregular. The pulsus bigeminus and the pulsus trigeminus are frequently observed; there is a disturbance of the harmonious co-operation of the inhibitory and the accelerator cardiac nerves. With still larger doses there may be a fall of blood-

pressure. Cyon concludes that these effects are due to the calcium phosphate and other salts from the concretions of the gland.

Dixon and Halliburton find, as might have been expected, that extracts of the pineal body, when intravenously injected, give a fall of blood-pressure (see Chapter III.). Extracts of the choroid plexus also bring about a lowering of the blood pressure. They find also that while extracts made from the choroid plexus of the ox, sheep, and man, injected into the sub-cerebellar cisterna, or the lumbar region, cause a flow of cerebro-spinal fluid, extracts of pineal body have no such effect.

Ott and Scott report, in addition to some changes in the blood-pressure, that pineal intravenous injection has a galactagogue action similar to, though less than, that of pituitary extract (see p. 353).

Jordan and Eyster in 1911 found on pineal injection a vasodilation in the intestines, a more forcible beat of the isolated cat's heart, diuresis and glycosuria. There was also increased depth of breathing for some time after the injection. The effects are comparatively slight.

Schäfer and MacKenzie (see Chapter XV.) could not confirm the observation of Ott and Scott as to the galactagogue action of pineal extracts. But MacKenzie in 1911 obtained a slight effect which he thought might be due to contamination with pituitary material by absorption from the cerebro-spinal fluid.

2. *Direct Stimulation of the Pineal Body*

Cyon appears to be the only observer who has used this method. He employed electrical stimulation applied to the pineal body of the rabbit and states that he could observe slight changes in the form and position of the gland. There was no alteration in colour, so that the effects could not be due to vasoconstriction. They were due, he thinks, to contraction of muscle, though, it must be observed, the existence of muscle fibres in the body is exceedingly doubtful. According to Cyon, these experiments point to a mechanical function on the part of the pineal body: it is suggested that it controls the inflow and outflow of cerebro-spinal fluid of the third ventricle. The part played by the pineal body in this regard is likened to that of the thyroid and the pituitary, and all three

are supposed to be concerned in regulating the intracranial pressure.

3. *Attempts to destroy the Pineal Body by means of the Cautery*

Sarteschi in 1910 had obtained negative results in a series of experiments upon rabbits.

Exner and Boese destroyed, by means of the thermo-cautery, the pineal body in ninety-five rabbits. Seventy-five per cent. of the animals died within the first twelve hours from bleeding into the ventricle. Twenty-two animals were kept under observation for some time. In six the authors thought the operation was complete, and the animals lived to sexual maturity. There was no sexual precocity. The authors concluded that in rabbits extirpation of the pineal body produces no noticeable effects. But, as we shall presently see, it is, in all probability, impossible to destroy completely the pineal body of the rabbit by this method.

4. *Extirpation of the Pineal Body*

Sarteschi attempted extirpation by ordinary surgical means in some of his rabbits ; but, although he thought that this was complete in one case, and that in this there was some retardation of development, yet the conclusion is not satisfactory.

Exner and Boese also made an attempt to remove completely the pineal body from rabbits by surgical means other than the cautery. They could not be certain that the operation produced any specific results.

Foà came to the conclusion that the rabbit is not a suitable animal for pineal extirpation. He turned his attention, therefore, to the chicken, and arrived at the following conclusions :—

1. Complete extirpation in the earlier months of life gives rise to a retardation of development during the first two or three months after the operation ; afterwards development of the body becomes normal.

2. In cockerels there is an earlier development of both primary and secondary sexual characters in the operated than in the control animals.

3. In cocks examined eight to eleven months after the operation there is marked hypertrophy of the comb and of the testes.

4. There are no corresponding changes in pullets.

These interesting results with cockerels received an important confirmation by Sarteschi, who had previously failed to extirpate the pineal body. Following the technique employed by Foà for chickens and first recommended by Lo Monaco (that is to say, by ligaturing the longitudinal sinus), Sarteschi succeeded in extirpating the pineal body in very young rabbits and dogs. In the males which survived the operation there was a notable hypertrophy of the testes, bodily overgrowth and sexual precocity—results quite comparable with those obtained by Foà in cockerels.

More recently Foà reports that pineal extirpation has no effect on female chickens or female rats. But upon male rats there is an effect comparable with that produced in cockerels, viz., a rapid increase in body weight and in size of the testes. He notes also an advanced development both of the spermatozoa and of the interstitial tissue of the testis, both in rats and cockerels. The premature increase of interstitial tissue, it is suggested, corresponds to the precocity of the secondary sexual characters—growth of comb in the cock and increase of body weight in the rat.

These observations are of the greatest interest and importance, and point very strongly to the view that the pineal gland exercises an inhibitory function upon sexual development before puberty. At this period an involution of the gland occurs.

5. *Effects of Castration upon the Pineal Body*

Although Sarteschi in 1910 had failed to find changes in the pineal body of animals castrated in early life, yet Biach and Hulles report that castration causes atrophy of the pineal. Castration is stated to have the contrary effect upon the pituitary body.

6. *Feeding Experiments*

Pineal feeding was suggested by Kidd in 1913, and the first actual experiments in this direction so far as I am aware, were carried out by Dana and Berkeley in the same year. These authors state that feeding guinea-pigs and young rabbits with pineal gland causes an increase in body weight, but the opposite effect is obtained in children.

McCord has studied the effects of pineal feeding upon chicks, dogs, and especially upon guinea-pigs. He finds that the effects usually attributed to pineal deficiency (hypopinealism) are obtained by supplying an increased amount of pineal substance by feeding or injecting pineal preparations. Such administration of pineal substances leads to a more rapid growth of body than normal, and determines an early sexual maturity. The excess in rate of growth was most pronounced in *young* animals fed with pineal tissue obtained from *young* animals. After maximum size was attained, pineal administration appeared to be ineffective. Both males and females respond, in rate of growth, to the influence of pineal substances, but the response has been more definitely manifested in males.

These observations, so far as the effects upon male guinea-pigs are concerned, have recently been confirmed by Horrax, and McCord and Allen find that pineal substance causes contraction of the melanophores in tadpoles.

Pathological Anatomy and Clinical Pathology

Cysts of the pineal have been known for a long time. Some of these are without characteristic effects; others give rise to serious symptoms.

Teratomata are very common. They were first fully described by Weigert, and have since received a considerable amount of attention.

Various other tumours of the pineal body have been described, such as glioma, sarcoma, carcinoma, and mixed growths.

There is now a general agreement among clinical pathologists that diseases of the pineal body are accompanied by a characteristic train of symptoms. It is curious that there is some degree of resemblance between these symptoms and those due to lesions of the pituitary body.

Our information upon the clinical symptoms in pineal disease is largely derived from the work of Marburg.

Hempel records a case of carcinoma of the pineal gland in which there was at the commencement obesity, but later very marked atrophy of the fatty tissues. In complete destruction of the body, which occurred in six cases of malignant tumour, there was a severe disturbance of the trophic functions (Biedl).

Marburg found a very striking obesity in a nine-year-old

girl who had the symptoms of a brain tumour. At the post-mortem examination a compound tumour of the pineal body was found. It is not certain whether the obesity is due to a hyper- or to a hypo-function of the gland. Marburg is inclined to the former view, but the preponderance of evidence is, perhaps, in favour of the latter (Biedl).

But there are other interesting conditions besides obesity found in patients with pineal tumours. These are found in young subjects. It has been found that in boys under seven years of age symptoms of brain tumour and disease of the corpora quadrigemina are associated with abnormal tallness, unwonted growth of hair, premature sexual and genital development, and early maturity. In these cases there is frequently found on post-mortem examination a teratoma of the pineal body. The symptoms just enumerated are generally supposed to be due to a hypofunction of the pineal gland. Frankl-Hochwart urges the importance of the symptoms mentioned as diagnostic of pineal tumours.

Pellizi has described the pineal syndroma as "macrogenitosomia præcox." There is a premature development of the genitals, which, particularly in regard to the volume of the penis, gives the appearance of an adult. The degree of development of the body and of the skeleton corresponds to that of an age five, ten, or twelve years more advanced. There is a premature ossification of the bones. The intelligence almost always corresponds to the age. In these cases one observes very frequently that there are symptoms of cerebral tumour and destruction of the corpora quadrigemina. The condition always becomes developed before the eighth year, and very frequently before the third, and is commoner in boys than in girls. The hereditary factor has no special influence on the causation. The pathogenesis seems to depend in most cases on a destructive lesion or growth of the pineal body.

In considering the results of clinical observation, it must be remembered that less than a hundred cases of tumours of the pineal gland have been recorded. In these cases two groups of symptoms have been described—the nervous and the metabolic. In adults only the nervous symptoms occur. In children, however, we get the metabolic disturbances, presumably due to an alteration in the secretory activity of the gland, and these are most marked in young males. They

consist, as we have seen, in precocious sexual and mental development. This precocity has usually been attributed to a hypopinealism, and this view was supported by the extirpation experiments. But, as we have seen, a similar precocity of development accrues from feeding with pineal substance. This fact introduces a complication which renders it impossible to reconcile the results of clinical observation and experimental work upon animals.

CHAPTER XVII

THE INTERRELATIONS OF THE ORGANS OF INTERNAL SECRETION

Although the allusions to a relationship between the organs furnishing internal secretions are so numerous, and although assumptions in regard to such relationships are very common in medical and surgical literature, yet it may be affirmed that the theories and suggestions which have been put forward are out of all proportion to the established facts and any certain knowledge of the subject.

In this chapter an attempt will be made to examine critically some of the current views in connection with this part of our subject, and, if possible, to separate out a portion at any rate of the grain from the heap of chaff.

The view is now so prevalent as to be almost universal among clinical workers that derangement of any one of the ductless glands leads to more or less evident disturbance in other members of the series. The phrase "polyglandular syndrome" has become a commonplace of medical literature. And investigators in the fields of experimental physiology and pathology have been so impressed by cases where the internal secretion of one organ appears to stimulate another to activity, that they have for the most part joined with the clinicians in regarding the organs of internal secretion as forming a system whose several functions are very intimately related to each other.

The arguments in favour of such a relationship between the ductless glands and other organs which yield internal secretions are derived from very many different sources, experimental and clinical. Although many of these relationships are referred to frequently in the literature, yet it is only within recent years that an attempt has been made to collect the evidence and state it in compact form. In the compilation of this

chapter I am indebted to an account of the subject written by Hoskins in 1911.

It is not always easy to determine from the phraseology employed precisely what kind of a system is alleged to be constituted by the association together of the various internally secreting glands. A recent writer says that the animal body is controlled by an "interlocking directorate" made up of the glands of internal secretion, while in modern expositions of the relations of the endocrinous organs we frequently find that the "system" is made to include not only the adrenal bodies, the thyroid glands, and the pituitary, along with the thymus, parathyroid, and pineal, but also the reproductive organs, the pancreas, liver, spleen, duodenum, small intestines generally, the stomach, the uterus, and the mammary gland. When we remember that certain authors refer to a "kinetic system" (which includes the brain, the thyroid, the adrenals, the liver, the pancreas, and the muscles), and that the whole of the sympathetic nervous system is supposed to be under the control of the chromaphil tissues, and that the carbohydrate metabolism of the body is alleged to be under the conjoint control of the central nervous system, the liver, the pancreas, the intestine, the chromaphil tissues, the thyroids and parathyroids, and the pituitary, it will be conceded that any attempt to express all the asserted possible relationships in diagrammatic form must result in failure.

A summary of the connections postulated in the last paragraph would amount to nothing less than a statement that the various organs and tissues of the body are functionally related to each other, and when the view is put forward that the secretion of one of the ductless glands produces an effect upon the nervous system as a whole or upon an important section of it, this amounts to the allegation that the gland in question exerts its influence upon practically the whole body. It may be possible in the future, when our knowledge of the ductless glands and indeed of physiology generally shall be considerably greater than at present and if current views as to the supreme directing influence of the internal secretions be confirmed and substantiated, to formulate some satisfactory theory according to which the organs of internal secretion dominate the whole of the bodily activities, normal and pathological.

In the present chapter no attempt will be made to cover the field just indicated ; it will be necessary to confine our attention to the known or reasonably suspected instances of influences exerted by one internally secreting gland upon others of the series, these influences being not always necessarily direct—as, for example, when the nervous system is called into play.

If there has been in many instances undue haste in formulating theories of the functions of individual glands, much more has this been the case in regard to theories of interrelationships. It is not certain that the clinicians have been greater offenders than the laboratory workers, though it must be confessed that many of the descriptions of syndromata which have been supposed to accrue from correlated disturbances of the endocrinous organs are based upon an inadequate conception of the actual physiological facts and therefore form a very unsatisfactory indication for treatment.

A priori and regarding the question chiefly from the morphological standpoint, it is doubtful if one would expect the various ductless glands to be related to each other. From a broadly comparative standpoint, it is very difficult to arrange these glands in a coherent series. There are reasons, fully explained elsewhere (p. 227 *et seq*), for regarding the thyroid, parathyroids and thymus (along with certain less important branchial cleft organs), as morphologically related. Some authors regard the thymus as closely related to the thyroids and parathyroids from a physiological as well as a morphological standpoint. The glandular portions of the pituitary body may possibly be included in this morphological group, but it must be pointed out that the origin of these different organs is not quite identical. The only common feature is that they arise from some part of the primitive alimentary canal or its vascular outgrowths, the gill clefts. The pituitary body arises from the ectoderm, while the branchial cleft organs are of entodermal origin.

The cortex of the adrenal body is a representative of a kind of tissue which is widely distributed in the region of the reproductive organs (see p. 116), and possibly it might be expected that the corpus luteum and the interstitial cells (as well as the rest of the elements) of the ovary and the testis might rank in the same group.

According to modern views, the chromaphil tissues form a series which may be regarded as sympathetic glandular organs and which are widely distributed along the course of the vegetative fibres.

The majority of writers still deal with the adrenal bodies as if they represented functional entities. But as far as is definitely known, the chromaphil tissues physiologically have nothing whatever to do with the adrenal system (or adrenal cortex and "accessory cortical bodies").

The pancreas, along with its islets of Langerhans, is an outgrowth from the alimentary canal, and so might be regarded as belonging to the same system as the branchial cleft organs.

We have not sufficient information to guide us to a decision as to whether we ought to regard morphological and embryological connections as an indication of a probable physiological relation.

Elliott quotes Gaskell as classifying together, on morphological grounds, the pituitary body, the thyroid and the adrenal cortex, being all modified from the coxal glands, that is, the segmental excretory apparatus of some primitive arthropod type. But Gaskell's theory, so far as the ductless glands are concerned, is open to grave criticism, and the theory as a whole is, I believe, not generally accepted by morphologists.

It must be remembered that a normal gland may either excite or moderate the activity of another. If an exciting organ be suppressed, there will be insufficiency of the second, and so we get a diminution of two functions. If a moderating organ be reduced in activity, the disturbance occurring in the second gland will be overaction. And further, one gland may exercise an exciting influence upon a second and a suppressing action on a third. In these actions both the sympathetic and the autonomic systems may take part.

The evidences in regard to endocrinous interrelationships are derived from pathological anatomy, from clinical observation, and from experimental investigations.

A. Interrelationships involving the Thyroid Gland

Action of the Thyroid upon the Adrenal Bodies

Sub-thyroidism has not been shown to have any effect upon the adrenal bodies, although attempts have been made to show

that thyroidectomy depresses the function of the chromaphil tissues.

The Viennese school has elaborated a very complicated theory. The thyroid and parathyroids are antagonistic to each other. While the former stimulates the sympathetic, the latter inhibits this system. The parathyroid is the ally of the pancreas in checking or inhibiting metabolism, while the adrenals and the thyroid increase it. So that when the thyroid is put *hors de combat* four things happen: (1) Loss of thyroid secretion, inducing slowed or diminished metabolism; (2) Absence of stimulation of the adrenals (that is to say, the chromaphil tissues); (3) Relaxation of the inhibition of the pancreas; (4) Diminished excitability of the nerves to the thyroid, that is, branches of the vagus.[1]

In regard to superthyroidism, there is some evidence that the amount of adrenin in the blood is increased in this condition. This evidence, though not very positive or great in amount, supports the theory that the secretion of the thyroid acts as a direct stimulant to the chromaphil tissues, causing them to yield adrenin to the blood in larger quantities.

There are grounds for extreme scepticism regarding all this work.

Cramer has put forward the view that the thyroid and the adrenal are part of an apparatus which controls the temperature of the body. He regards the adrenal as a gland in itself and not as consisting of two independent constituents. One of its functions is to act with the thyroid as a humoral mechanism regulating body temperature, and supplementing the action of the nervous system. The thyroid hormone mobilizes liver glycogen by increasing the production of adrenin and sensitizing the sympathetic nerve-endings. At the same time adrenin constricts the arterioles of the skin, thereby diminishing the loss of heat from the body. Cramer has adduced a number of experimental and pathological observations in support of this theory.

Relations between the Thyroid and Pituitary Bodies

Clinical evidence as to pituitary hypertrophy as a result of thyroid deficiency is unsatisfactory, but the experimental

[1] It is more usually admitted that the specific nerves to the thyroid are derived from the sympathetic (see p. 308).

evidence is convincing. As we have already seen (p. 366), a very striking effect is caused by removal of the thyroid upon the pituitary body, which not only undergoes general enlargement, but exhibits well-marked indications of increased secretion.

There is, however, no increase in the amount of iodine in the hypertrophied pituitaries in these cases, so that a true vicarious functioning seems out of the question.

How far the parathyroids may be concerned in this question we do not know. According to Halpenny and Thompson, some of the alterations which have been described in the pituitary occur when the parathyroids only are extirpated. But other observers have failed to find any changes in the pituitary after parathyroidectomy.

When the pituitary hypertrophies as a result of subthyroidism, there are no symptoms of superpituitarism. So that the pituitary as a whole does not become more active.

Relations between the Thyroid and the Reproductive Organs

Many of the changes found in various organs of the body as a result of thyroidectomy are not to be attributed directly to a loss of the thyroid secretion, but to the effects of intoxication and troubles of metabolism which supervene in these cases.

In the female the thyroid is known to become enlarged at puberty, at the menstrual periods, and during pregnancy. In animals from whom the thyroids have been removed at an early age, the reproductive organs are late in developing or develop in an imperfect manner, so that we have a condition of sexual infantilism. Some changes in the reproductive organs have also been recorded in cases where thyroidectomy was carried out in the adult.

In exophthalmic goitre the sex functions are often affected (menstrual disturbances); and there is sometimes atrophy of the genital organs. In myxœdema there may be complete impotence. The theory that the thyroids have a stimulating effect on the reproductive organs has therefore some evidence to support it.

Some authors claim to be able to diagnose thyroid deficiency in cases of incomplete sexual development and to remedy the defect by thyroid medication.

Action of the Thyroid on the Thymus

For the anatomical and embryological relationship between thyroid and thymus see p. 277 *et seq.* The thyroid secretion affects the growth of the thymus gland, which has been found to undergo an increase in size in fœtal animals after thyroid feeding of the pregnant mother (guinea-pigs). In exophthalmic goitre the thymus is often hypertrophied and has been supposed to take a part in producing the symptoms of the disease. But not only in Graves's disease does thymus hypertrophy occur ; it may also be associated with simple congenital goitre. It is not clear whether thyroidectomy causes thymus atrophy.

Action of the Thyroid on the Pancreas

It is well known that the thyroid has some influence on carbohydrate metabolism, and this is often explained as indicating a relation between the thyroid and the pancreas. But Krause and Cramer find that when small amounts of fresh thyroid gland are administered for two or three days to rats or cats fed on a carbohydrate-rich diet, the liver will be found to contain only traces of glycogen. This effect is due to an inhibition of the glycogenic function of the liver, not to an increased utilization of carbohydrates. It is not accompanied by glycosuria, and (in dogs) the tolerance for glucose is only slightly diminished by thyroid feeding.

If the parathyroids are removed also, the assimilation limit for sugar is distinctly lowered and the injection of adrenin then produces more pronounced glycosuria than in the normal animal. This is usually quoted as one of the instances of an antagonistic action between thyroids and parathyroids. The experiments involving removal of thyroids without the parathyroids are notoriously difficult, and much further evidence is required on the subject.

Some observers have reported an increase in the islets of Langerhans after thyroidectomy.

Notwithstanding the meagre character of the evidence, the majority of modern writers seem fully to accept the view that the thyroid has a direct inhibitory influence upon the pancreas, and affects carbohydrate metabolism through the internal secretion of this organ.

Summarizing the effects of the thyroid upon the other endocrinous organs, we may state that there is some evidence that it stimulates the chromaphil tissue to increased activity. There is clear evidence that subthyroidism causes hypertrophy of the pituitary and this is supposed to indicate some kind of vicarious function. It seems clear that while the thyroid has a marked influence upon general metabolism in the young animal, it has a very special influence upon the development and growth of the reproductive organs. The direct effects of thyroid upon thymus are doubtful. The alleged action of thyroid upon the pancreas can only be proved or disproved when our knowledge of carbohydrate metabolism has considerably increased. At present there seems no reason to believe that the effects of thyroid upon such metabolism are wholly or in part due to a direct effect upon the internal secretion of the pancreas.

B. **Interrelationships involving the Pituitary Body**

Action of the Pituitary Body upon the Thyroid

Some recent writers express their belief that a decided antithyroid influence is exerted by the substance ("tethelin" Robertson) secreted by the anterior lobe of the pituitary.

Superpituitarism (by feeding or injection with pituitary substance) is said to cause thyroid hypertrophy, but this is doubtful.

Apituitarism or subpituitarism is alleged by Cushing to cause hypertrophy of the thyroid. Exner has confirmed this so far as surgical experience in the human subject is concerned. We have seen that extirpation of the thyroid causes hypertrophy of the pituitary. A possible vicarious activity of the two glands has already been discussed.

Action of the Pituitary Body upon the Reproductive Organs

It seems clear that certain cases of infantilism are associated with lesions of the pituitary body. Although there has been some discussion as to whether these defects are due to super- or sub-pituitarism it seems from a consideration of the most recent investigations that they are the result of the latter condition. The usually accepted view is that the pituitary

normally supplies a secretion which stimulates the sex glands to activity.

As bearing upon the relationship between the pituitary and the sexual functions, the work of Erdheim and Stumme is of great interest. These authors describe three types of cell in the glandular part of the pituitary :

1. Eosinophile granular cells (chromophile 1 ; acidophile).
2. Basophile granular cells (chromophile 2 ; basophile).
3. "Hauptzellen" (chief cells ; chromophobe cells) (see p. 339).

The chief cells have very badly defined and poorly staining protoplasm. In pregnancy the pituitary may become hypertrophied to two or three times its normal size. The increase consists entirely in the glandular portion. There are no longer to be seen either chromophile or chromophobe cells, but there are peculiar large, finely granular cells (the "pregnancy cells"). These are derived from the chief cells, which grow from the centre of the alveolus, and occupy a large part of the secretory structure. These slowly retreat again during the period of involution.

The pituitary during pregnancy resembles an epithelial tumour. The increase in the amount of secretion is seen by the fact that one can squeeze a milky juice out of the gland. The hypertrophy persists to a certain degree, even after pregnancy, so that the weight of the gland in a multipara may be three times as great as that of a normal gland.

Erdheim and Stumme thought that the hypersecretion of the pituitary in pregnancy is manifested by an enlargement of the hands and lips which is sometimes observed. Occasionally, also, there may be more striking symptoms, due to the effects of the pituitary tumour. Among these may be mentioned hemianopia.

Mayer is of opinion that the pituitary changes are due to functional changes in the ovary—in other words, that the pituitary may function vicariously for the ovary. A relation between pituitary and ovary is shown by the fact, already mentioned, that in castrated women and animals there is frequently enlargement of the pituitary. Further, after destructive diseases of the reproductive glands the pituitary reacts by hypertrophying. Mayer is even inclined to believe

that the actual commencement of the mischief in acromegaly may be situated in the reproductive organs.

Action of the Pituitary Body upon the Adrenal Bodies

Certain French observers have described hyperplasia of the adrenal cortex after feeding with pituitary substance. Gottlieb has shown that extracts of the posterior lobe of the pituitary and of the chromaphil tissues mutually assist the action of one another upon the bloodvessels. Thus an injection of a small dose of adrenin will increase the subsequent effect of a dose of pituitrin, and *vice versâ*. It is also stated that an excess of adrenin is poured out into the blood-stream as the result of an injection of extract of the posterior lobe of the pituitary. The evidence for a direct action of pituitary upon either the chromaphil tissue or the adrenal crotex is not, however, very convincing.

Action of the Pituitary Body upon the Pancreas

How far the facts before us point to a direct action of the pituitary upon the pancreas is doubtful. We know that subpituitarism leads to an increased sugar tolerance. According to Cushing, this depends upon the function of the posterior lobe. Animals from whom this lobe has been removed will not develop glycosuria when the pancreas is extirpated. But the production of glycosuria by removal of the pancreas is due to an action on the liver.

Glycosuria occurs in acromegaly, and this has been supposed to be due to changes in the pancreas. The evidence on this point is unsatisfactory.

Many authors believe that there is some kind of functional correlation between pituitary, chromaphil tissue, pancreas, liver, and thyroid, so that any interference with the function of any one of them may affect the carbohydrate metabolism through its influence upon the others.

To sum up the influence of the pituitary upon the other ductless glands it may be definitely affirmed that the organ has some influence upon the growth of the reproductive organs, but the evidence for a direct effect upon the thyroid, adrenals, and pancreas is much less convincing.

C. Interrelationships involving the Adrenal Bodies (Chromaphil Tissues and Adrenal Cortex)

Action of the Adrenal Bodies upon the Gonads

An important connection between the adrenals and the reproductive organs has long been recognized. The main facts are given in another chapter (see Chap. XI). In this place we need only remind the reader of the frequent association between sex anomalies and tumours of the adrenal cortex. It is stated also that vigour of reproduction is reduced by partial adrenal extirpation. The theory is that the cortex of the adrenal body stimulates the growth of the reproductive organs, especially in the male.

So far as I am aware, there are no observations which point to any direct connection between the adrenal medulla or other chromaphil tissues and the sex organs.

Action of the Adrenal Bodies upon the Thymus

Hypertrophy of the thymus has been recorded in cases of Addison's disease, and the association of adrenal hypoplasia and thymus hypertrophy is said to be common in *status lymphaticus*. There is also some experimental evidence that adrenal deficiency is frequently associated with hypertrophy of the pancreas.

Action of the Adrenal Bodies upon the Pituitary

At present there is little evidence of any relationship of the adrenals to the pituitary.

Action of the Adrenal Bodies upon the Thyroid

Hypertrophy of the thyroids has been reported in some cases after extirpation of the adrenals, but we have not sufficient data to justify any statement as to a direct action of the former organ upon the latter.

Action of the Adrenal Bodies upon the Pancreas

This matter has already been discussed in the chapter devoted to the adrenal bodies (see Chap. XI.).

Here it is only necessary to point out that the whole of the effect of the adrenal bodies upon carbohydrate metabolism is

not exerted through the pancreas, but part must be directly on the liver. As we have previously seen (p. 162), adrenin has a direct effect on the glycogen storage of the liver.

We have then considerable evidence that the adrenal cortex stimulates the growth of the gonads, and some little evidence that adrenal hyperplasia induces overgrowth of the thymus. The most usual theory as to the relation of the adrenal body to the pancreas is that the former inhibits the latter. According to some observers, this effect is not direct, but related to an action on the vasoconstrictor nerves.

D. Interrelationships involving the Organs of Reproduction

Action of the Reproductive Organs on the Pituitary Body

Several authors report that pregnancy causes increased activity of the pituitary gland. But it has been pointed out that this may be simply a reaction to the changed metabolic conditions obtaining during pregnancy. Castration in both sexes is followed by hypertrophy of the anterior lobe of the pituitary body. There seems to be a special overgrowth of the eosinophile elements.

Recent investigations lends support to the view that it is the loss of the internally secreting elements of the testes (the interstitial cells of Leydig) which leads to hypertrophy of the pituitary body.

These observations indicate that the pituitary body is normally held in check by the secretions of the reproductive organs. When the inhibition is removed the pituitary shows increased activity leading to overgrowth of different parts of the body, as in acromegaly and after castration (Hoskins).

Action of the Reproductive Organs on the Thymus

The thymus normally persists till puberty, when the reproductive organs grow. *A priori*, castration would tend to prolong the period of persistence of the thymus. This has been found experimentally to be the case. The work of Calzolari, Henderson, and Goodall in this direction is referred to in Chap. XIV. The sex glands then tend to exert a depressant effect on the thymus.

Action of the Reproductive Organs on the Adrenal Bodies

During pregnancy there is a distinct enlargement of the adrenal bodies. This chiefly affects the cortex, but there is some growth of the medulla also (Elliott and Tuckett). What is the mechanism or what the significance of this overgrowth is not known.

Action of the Reproductive Organs on the Thyroid

A direct influence of ovary and testes upon the thyroid body is not known to exist.

It appears probable, then, that deficiency of the sex organs leads to hypertrophy of the pituitary body possibly by removing a normal check upon it. Activity of the sex glands seems to lead to depression of the thymus. The influence of the gonads on the adrenal and thyroid bodies is of a doubtful nature.

E. **Interrelationships involving the Thymus**

Activities of the thymus upon the gonads and upon the thyroids have been alleged, but the experimental evidence is not conclusive.

F. **Other Interrelationships**

In regard to the influences exerted upon the other endocrinous organs by the pancreas, the parathyroids and the pineal body, there is little that need be said here. There is little direct evidence that the pancreas does actually depress the thyroid, though this supposition is an important part of the theory of the Vienna school. The relation of the parathyroids to the thyroid is sufficiently discussed in Chapter XIII. and the relations of the pineal to the organs of reproduction in Chapter XVI.

The "Pluriglandular Syndrome"

Within recent years a great deal has been written about what is called the "pluriglandular syndrome." The general conception which has been evolved is by no means definite. But in general terms it may be stated as follows. In

diseases affecting the glands of internal secretion it is very common (perhaps even the rule) that more than one of these glands are from time to time or simultaneously involved. The nature of the clinical picture produced depends upon the preponderance of symptoms arising from disorder of one or more of the glands in question whose dysfunction results in recognizable changes.

Lereboullet classifies pluriglandular disorders as follows: (1) A primary change in one gland with secondary disorders in one or more, *e.g.* Graves's disease, with ovarian insufficiency and amenorrhœa; (2) Association of two uniglandular syndromes, *e.g.* myxœdema and acromegaly; (3) Association of several uniglandular syndromes without predominance of any one. The last condition may be due to syphilis or tubercle and affects commonly thyroid, testis, and adrenal.

Timme has recently described a condition depending upon disease of thymus, adrenal, and pituitary in combination. He says that this condition is frequently met with and that its various stages are easy of recognition. The chief symptoms are extreme liability to fatigue, a low blood-pressure, headache, and inordinate growth of the whole body. A restoration to a normal condition, or to something which approaches this, may be brought about spontaneously by compensatory overgrowth and overactivity of the pituitary. Feeding with pituitary extracts is the treatment which is found to be most beneficial.

Pubertas præcox apparently may arise from affection of the whole ductless gland system, but primarily from the reproductive organs, pineal and adrenal cortex. The majority of cases are probably due to some affection of the gonads; next in frequency are cases apparently due to tumours of the pineal and finally we have those due to growths in the adrenal cortex. It is stated that pineal types occur mostly in the male, the adrenal and gonadal in the female.

Dercum's Disease, or *Adiposis dolorosa*, has been included by some writers in this group. It is characterized by irregular, sometimes symmetrical, deposits of fatty masses in various portions of the body, preceded by and attended with pain. It occurs mostly in middle-aged women. There may be a history of alcohol, syphilis, rheumatism, or bodily injury. The fatty masses are of variable size and distributed on the trunk and

extremities. The pain is sometimes spontaneous, sometimes induced by manipulation. The new fatty tissue has a soft feel, or there may be harder tumours. Hæmorrhages from mucous surfaces may be observed. The disease is chronic and progressive.

The morbid anatomy consists in an increase of fatty and connective tissue and degenerative changes in nerves. The thyroid has been found hard and calcareous. Dercum's disease differs from other forms of obesity in its irregular distribution, in the presence of pain, and sometimes of impaired sensibility. It differs from myxœdema in that face, hands, and feet are not affected and in the absence of mental symptoms.

Thyroid treatment is said to do good in some cases (Allbutt).

Arachnodactyly.

Some seven or eight cases have been described under this name, notably by Morvan and Poynton. The patients are children with overgrowth of the long bones, phalanges, metacarpals and metatarsals. The growth of bone is out of proportion to that of muscles and tendons; so that contractures are produced.

It is possible that the condition may be due to some defect in the organs of internal secretion.

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